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SATURDAY FEBRUARY 2 1957

TABLE OF CONTENTS

Clinical Picture of Pernicious Anaemia Prior to Introduction of Liver Therapy in 1926 and in Edinburgh Subsequent to 1944 Sir STANLEY DAVIDSON, M.D., F.R.C.P.Ed., F.R.C.P. 241

Clinical Significance of Weight Trends During Pregnancy A. M. THOMSON, M.B., D.P.H., and W. Z. BILLEWICZ, M.SC. 243

Calcium Metabolism and Bone Changes in Sarcoidosis GORDON MATHER, M.D., M.R.C.P. 248

Anaesthesia for Aortic Reconstruction HARRY L. THORNTON, F.F.A. R.C.S., D.A. 253

Canicola Fever in Man Through Contact with Infected Pigs JOYCE D. COGHLAN, PH.D., B.SC., JOHN NORVAL, M.R.C.V.S., and H. E. SEILER, M.D., F.R.C.P.Ed., D.P.H. 257

Noradrenaline in Shock Due to Visceral Perforation D. D. DAVIES, M.R.C.S., L.R.C.P., D.A. 261

Report of Two Siblings Diagnosed as Cases of Acute Lymphatic Leukaemia MARY E. CARTER, M.B. 265

Two Cases of Rupture of the Extrahepatic Bile Ducts JOHN A. MCCREDIE, F.R.C.S., F.R.C.S.Ed. 267

The Antibacterial Activity of Chlorophyll SHEILA MOWBRAY, B.A. 268

MEDICAL MEMORANDA

Rupture of the Uterus Involving the Bladder. M. A. MAJEKODUNMI, M.D., F.R.C.P.I., M.A.O., D.C.H. 270

Perforated Duodenal Ulcer Complicating Prednisolone Therapy. E. V. HESS, M.B., and M. E. MACPHERSON, M.B. ..271

BOOK REVIEWS 272

GENERAL ARTICLES AND NEWS

Isaac Buxton (1773-1825). V. C. MEDVEI, M.D., M.R.C.P. 279

REPORTS OF SOCIETIES 280

MEDICAL NOTES IN PARLIAMENT 292

VITAL STATISTICS 293

MEDICAL NEWS 295

BIRTHS, MARRIAGES, AND DEATHS 296

QUESTIONS AND COMMENTS 297

OBITUARY

C. L. Gimblett, M.D., F.R.C.S., M.R.C.P. ..288

J. D. Benjafield, M.D., D.P.H. 288

Charles Noon, O.B.E., F.R.C.S. 289

P. S. Fleischman, M.D. 289

L. Dejardin, M.D. 290

Kiyoshi Shiga 290

Lewis M. Terman, PH.D. 291

J. G. Bird, M.D. 291

W. A. M. Swan, L.R.C.P.I. 291

Kathleen Hanby, M.B. 291

LEADING ARTICLES

Pathogenesis of Rheumatic Endocarditis 273

Living with a Colostomy 274

ANNOTATIONS

Fatal Reactions to Local Anaesthetics ..276

Mumps Orchitis 276

Torulosis and Hodgkin's Disease 277

Nomenclature of Blood-clotting Factors 278

CORRESPONDENCE

Two New Human Genes. L. S. PENROSE, M.D., F.R.S. 282

Translumbar Aortography. J. B. CLELAND, CH.M. 282

Toxic Psychosis Caused by "Preludin." L. CLEIN, M.B. 282

Glycyrrhetinic Acid. J. SOMMERVILLE, F.R.F.P.S. 282

SUPPLEMENT

Full Contents on First Page of Supplement

Remuneration Claim 47

Occupational Health Committee 47

Correspondence:

Remuneration Claim. B. SUGDEN, M.B.; M. B. LEITCH, M.B.; A. C. G. ROSS, M.B.; N. D. WAYNE, M.R.C.S.; G. H. PEARSON, M.B. 48

Medical Broadcasts. W. STODDART, M.R.C.S. 49

CORRESPONDENCE—*contd.*

Herpes Zoster and Chicken-pox. G. MELOTTE, M.B. 283

Drug Sensitivity Presenting as Penile Herpes. W. A. BROWN, M.D.; F. G. MACDONALD, M.R.C.S. 283

Neostigmine-resistant Curarization. J. A. SCANLON, M.B. 283

Psychiatry in Africa. A. S. HENDERSON, M.B. 283

Common Infectious Diseases in General Practice. J. G. P. POWER, M.B. 284

Tonsils and Adenoids. P. HUGGILL, F.R.C.S.; J. D. TRETHOWAN, F.R.C.S.; L. G. JACOB, M.B.; L. A. NICHOLS, M.R.C.S. 284

Sudden Infant Deaths. E. S. DUTHIE, M.B., and R. A. GOODBODY, M.D. 285

Bolus Obstruction. R. J. WILLIAMS, F.R.C.S. 285

Advertisements for Cigarettes. J. P. ANDERSON, M.D. 285

Carcinoma of Cervix and Corpus Uteri. H. E. HARDING, D.M. 285

Congenital Absence of Spleen. N. E. FRANCE, M.B. 286

Pregnancy Sickness. R. L. H. FLYNN, M.B. 286

Incidence of Diphtheria. H. I. WINNER, M.D. 286

Rupture of Hind-waters and Haemorrhage. H. FITZGIBBON, M.D. 286

Letters on other subjects appear on p. 287

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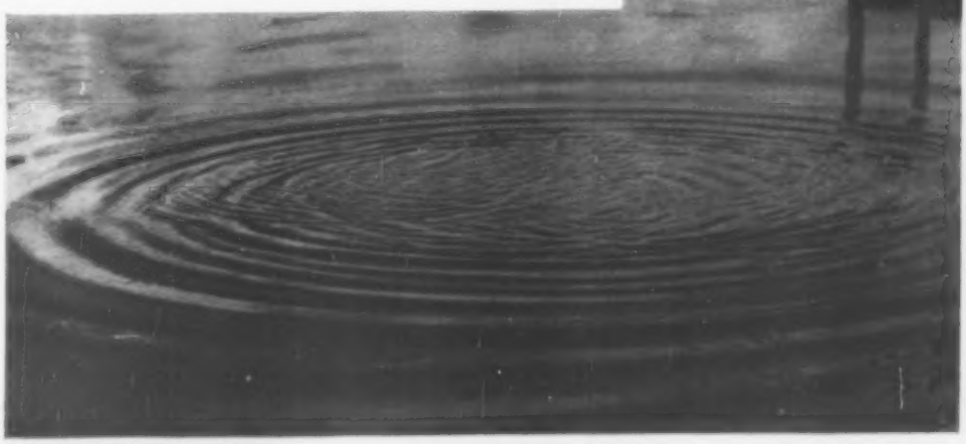

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 2 1957

CLINICAL PICTURE OF PERNICIOUS ANAEMIA PRIOR TO INTRODUCTION OF LIVER THERAPY IN 1926 AND IN EDINBURGH SUBSEQUENT TO 1944

BY

Sir STANLEY DAVIDSON, M.D., P.R.C.P.Ed., F.R.C.P.

Professor of Medicine, University of Edinburgh; Honorary Physician to H.M. The Queen in Scotland

Thirty years have elapsed since Minot and Murphy (1926) published their historic report on the value of liver in the treatment of pernicious anaemia. With each passing year fewer and fewer physicians remain on the staffs of the teaching hospitals who have had personal experience of the clinical features and course of pernicious anaemia in the era prior to the introduction of liver therapy. During the period 1920–7, first as assistant and then as a lecturer in the Department of Medicine, University of Edinburgh, I had ample opportunity of observing the tragic and inevitably fatal termination of the disease in large numbers of patients admitted to the wards of the Royal Infirmary under the charge of my chief, Professor G. L. Gulland, a famous haematologist.

I believe that the number of persons suffering from pernicious anaemia at the present time is much greater than it was when I first became interested in the disease 36 years ago. Hence the importance of early and correct diagnosis. There are two main reasons for this increased incidence. Firstly, the introduction of liver extract and later of vitamin B_{12} has enabled patients suffering from Addisonian pernicious anaemia to have a normal expectation of life. Secondly, at the present time there are many more people in the world within the age group 60–80 than there were at the beginning of the twentieth century, and therefore the number of persons who are liable to develop Addisonian pernicious anaemia is correspondingly greater. It has also seemed to me that certain clinical features present in the late stages of pernicious anaemia in the pre-liver era occurred so frequently and were so striking in character that they have continued to be reported as being of considerable diagnostic value, when in reality they are now of very limited importance in this respect.

Before this view could be accepted it would be necessary to demonstrate that the clinical picture of pernicious anaemia at the present time is in fact different from that seen prior to the discovery of liver therapy. Accordingly, I examined the records of 250 cases of pernicious anaemia which had been under my charge in Edinburgh during the period 1944–56 and compared them with the clinical features recorded in patients investigated prior to 1926: (1) by Davidson and Gulland (1930) in Edinburgh; (2) by Richard C. Cabot (1908) (in preparing this article Cabot stated that he had studied the case records of (*a*) 337 patients under his charge in private and hospital practice, (*b*) 320 case records collected from his medical friends in different parts of America, and (*c*) 543 cases selected by him after critical study of the literature, making a total of 1,200 cases); and (3) by Panton, Maitland Jones, and Riddoch (1923), who analysed 117 cases of pernicious anaemia admitted to the London Hospital between 1911 and 1920.

Age of Onset and Duration of Symptoms

Fig. 1 clearly shows that the age of onset of the disease is much later at the present time than it was 50 years ago. Thus more than 50% of the patients in the Edinburgh series (1950–6) developed the disease when over 60 years of age, as compared with only 10% in Cabot's series (1908). There can, however, be little doubt that this figure of 10% underestimates the true incidence. Cabot states that he included in his series 35 cases of the megaloblastic anaemia associated with pregnancy, a condition which develops in young women. In addition, some cases of the megaloblastic anaemia due to malabsorption must have been mistaken for Addisonian pernicious anaemia. Lastly, since diagnosis was much less accurate 50 years ago than it is at the present time, it would seem probable that the inclusion of cases of macrocytic anaemia due to aplastic, haemolytic, or leukaemic disease was partly responsible for the high incidence of "pernicious anaemia" stated by Cabot to occur under the age of 40 years.

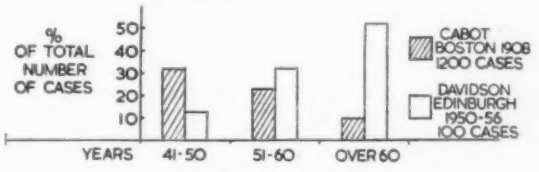

FIG. 1.—Age of onset.

TABLE I.—*Duration of Symptoms*

	Pre-Liver Series		Edinburgh Series 1944–56 Davidson 250 Cases
	1908 Cabot, Boston 1,200 Cases	1923 Panton, London 117 Cases	
Duration of symptoms before medical advice was sought	"Disability extending back for years"	Average 17 months	26% < 3 mths. 56% < 6 mths. 75% < 12 mths.

Table I indicates that the duration of symptoms prior to diagnosis is much shorter to-day than it was in the pre-liver era. Cabot states that many of his cases had symptoms

"extending back for years," and Panton states that the "average duration of the illness was 17 months prior to admission to hospital." Symptoms had been present for less than six months in 50% of the Edinburgh series (1944–56) and under one year in 75% of the cases.

Sex Incidence

Fig. 2 shows that in Cabot's series (1908) the disease affected males twice as often as females, whereas in an Edinburgh series of 600 cases seen during the period 1938–56

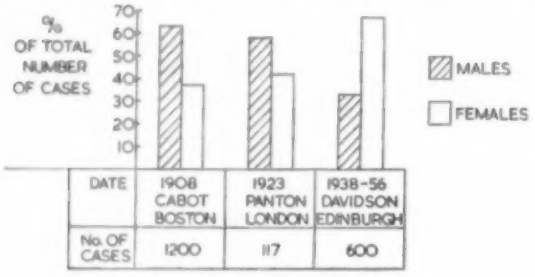

FIG. 2.—Sex incidence.

females were affected twice as often as males. A recent analysis of 223 cases examined in Glasgow showed an incidence of three females to one male (personal communication from Professor L. J. Davis). Wintrobe (1951) states that in the United States of America and in England males have been more frequently the victims of this disease than females, but in Germany and the Scandinavian countries the opposite has been recorded.

Symptoms

All authorities agree that the onset of the illness in the great majority of cases of pernicious anaemia is extremely insidious. This is as true to-day as it was 50 years ago. Patients continue to work for a surprisingly long time after the development of the disease before consulting their doctors. In addition, the anaemia is often much more severe than would be expected by the appearance of the patient or from a study of his symptoms. Table II shows

TABLE II.—*Symptoms*

	Pre-Liver Series		Edinburgh Series 1944–56 Davidson
	1908 Cabot, Boston	1923 Panton, London	
No. of cases	1,200	117	250
Weakness and tiredness	96%	91%	90%
Dyspnoea	88%	—	70%
Sore tongue	43% (of 372 cases)	24% (of 34 cases)	25%
Diarrhoea	51%	26%	9%
Constipation	35%	—	16%
Paraesthesiae	100%	—	38%

that the two symptoms most commonly encountered in pernicious anaemia, both in the pre-liver era and at the present time, are *general weakness and tiredness*, and *dyspnoea on effort*. The third most frequent symptom is the feeling of numbness and tingling in the hands and feet (*paraesthesiae*). This symptom, however, occurs much less frequently now (38% of cases) than it did 50 years ago (approximately 100% of cases), as indicated in Table II. This is also true of *soreness of the mouth and tongue*, which was present in 25% of the Edinburgh series as compared with 43% of Cabot's series. Davidson and Gulland (1930) stated that this feature was present in approximately half of their cases.

While indefinite symptoms referable to the digestive tract, such as poor appetite and vague abdominal discomfort, are frequently encountered in patients with pernicious anaemia, *diarrhoea* occurred in only 9% of the Edinburgh series. This is in marked contrast to Cabot's series, in which it was a notable feature in 51% of cases. Davidson and Gulland (1930) also state that diarrhoea occurred in approximately half of their cases at some stage of the illness. At the present time the complaint of constipation is twice as frequent as that of diarrhoea.

Signs

Apart from *pallor* of the mucous membrane and the skin, the most common finding in the Edinburgh series was a *pale smooth tongue* which was also moist and very clean. This was noted in no less than 64% of cases (see Table III).

TABLE III.—*Signs*

	Pre-Liver Series		Edinburgh Series 1944–56 Davidson
	1908 Cabot, Boston	1923 Panton, London	
No. of cases	1,200	117	250
Fever	79%	71%	22%
"Icterus"	Most cases	—	Uncommon
Acute glossitis (red and ulcerated)	42% (of 372 cases)	—	5%
Chronic atrophic glossitis (pale and smooth)	—	—	64%
Splenomegaly	27%	18%	8%
Spinal cord damage	11%	—	7%
Ataxic type	7%	—	6%
Spastic type	4%	—	1%
Peripheral blood:			
<2 million R.B.C./c.mm.	86%	Average 1·39 million	58%
<1 million R.B.C./c.mm.	21%		1%

No percentage figure for this sign is available in Cabot's or Panton's series, nor in Davidson and Gulland's monograph (1930). An extraordinary cleanness of the tongue in pernicious anaemia has, however, been mentioned by many authorities as being a common feature, and this sign is undoubtedly the result of atrophy of the papillae and mucous membrane of the tongue (*chronic atrophic glossitis*). *Acute glossitis*, indicated by a beefy-red, painful, and often ulcerated tongue, was reported as being present in patients in the pre-liver era in up to 50% of cases, in contrast to only 5% of the Edinburgh series. The second most common sign in the Edinburgh series was *fever*, which was present in 22% of the cases, in contrast to 79% in Cabot's series. The frequency and degree of fever is related to the severity of the anaemia, and the pyrexia disappears when the blood supply to the heat-regulating mechanism of the brain is improved by blood transfusion or as a result of treatment.

Icterus was another sign to which much attention was paid in the pre-liver era. Cabot rightly says that it is doubtful if the waxy yellow colour of the skin, which is such a notable feature of pernicious anaemia in severe relapse, is actually due to jaundice. Be that as it may, I am certain that this appearance of the skin is much more rarely seen at the present time than it was in the era before the discovery of liver therapy.

Minor degrees of *splenomegaly*—that is, the tip of the spleen being just palpable below the costal margin—were common in the pre-liver era. According to Cabot the spleen was palpable in no less than 27% of cases, but in the Edinburgh series it could be felt in only 8%. Gross enlargement of the spleen is so uncommon in pernicious anaemia that its presence should give rise to suspicion that the diagnosis is incorrect.

The *neurological features* of pernicious anaemia have always excited much interest. The name subacute combined degeneration of the cord was adopted to describe the lesions of the posterior and lateral columns of the cord which were so commonly present in patients dying of pernicious anaemia in the pre-liver era. The name is unsatisfactory in that the disease usually starts insidiously and not subacutely, combined lesions are often absent, and no cognizance is taken of the fact that lesions of the peripheral nerves occur much more frequently and much earlier than lesions of the central nervous system. If the name subacute

combined degeneration of the *cord* is to be retained it would appear logical to limit its use to lesions of the central nervous system. Unfortunately, even neurologists find it difficult to decide on the clinical features which clearly distinguish lesions of the posterior columns of the cord from lesions of the peripheral nerves. It is generally agreed that tendon reflexes, vibration sense, and positional sense may be reduced or absent and also that ataxia may be present in both conditions. There appear to be no infallible criteria which will distinguish the two lesions except histological examination of the affected structures.

Accordingly, the differential diagnosis during life has to be made on the basis of certain suggestive findings. Thus, hyperalgesia of calf muscles strongly supports the diagnosis of peripheral neuritis, while loss of vibration sense extending up to the pelvis favours a lesion of the posterior columns. Lastly, a markedly disproportionate increase in the degree of impairment of muscle and joint sensibility and vibration sense on the one hand, as compared with the degree of loss of superficial sensations of touch and pinprick on the other, supports the view that the posterior columns are affected. The presence of an extensor plantar response (positive Babinski sign) clearly indicates that a lesion of the central nervous system is present, but it must be remembered that in pernicious anaemia the lateral columns of the cord are affected much more rarely and usually much later than are the posterior columns. It should also be noted that peripheral neuritis may be due to a specific deficiency of vitamin B_{12} or it may result from anoxaemia of the peripheral nerves as a consequence of anaemia and cardiac weakness. In the former case it may be present when anaemia is minimal in degree and it will respond dramatically to vitamin B_{12} therapy. In the latter case it may occur in association with any form of anaemia, but only if the degree of anaemia is sufficiently severe, and it will not respond to vitamin B_{12} therapy, but will disappear when the haemoglobin level is raised by any method, including blood transfusion.

In assessing the incidence of subacute combined degeneration of the cord in the Edinburgh series of 250 patients, cases have not been included in which the only neurological features were of paraesthesiae and the subjective sensation of unsteadiness, since both these symptoms can be due to causes other than disease of the nervous system. Patients were classified as having involvement of the posterior columns if ataxia was a prominent feature, if tendon reflexes and positional sense were reduced or absent, and if vibration sense was lost as high up as the pelvis. They were classified as having lesions of the pyramidal tract if a spastic gait was present with increased tendon reflexes, extensor plantar response, and a greater or lesser degree of paralysis. These groups are therefore comparable to the two groups described by Cabot (1908) as the "ataxic type" and the "spastic type." Table III shows that involvement of the central nervous system was present in only 11% of Cabot's series and in 7% of the Edinburgh series. This is in contrast to the frequency of occurrence of paraesthesiae as indicated in Table II.

One of the most striking features of Table III is the difference in the degree of anaemia present in the three series when medical advice was first sought. Whereas 21% of Cabot's series had a blood count of less than one million red cells per c.mm., only 1% of the Edinburgh series had a similar degree of anaemia. Panton's series also showed a very high incidence of severely anaemic cases, the average red cell count being 1.39 million per c.mm.

Summary and Conclusions

Evidence is presented to show that the clinical picture of pernicious anaemia is very different to-day from that seen prior to the introduction of liver therapy. This difference is due to the fact that as a consequence of the improved facilities for early diagnosis and treatment which are now available the degree of anaemia in patients seeking medical advice at the present time is much less than was the case fifty years ago. Hence it is not surprising that certain clinical features which were held to be of particular diagnostic importance in the pre-liver era—namely, jaundice, splenomegaly, acute glossitis, diarrhoea, and subacute combined degeneration of the cord—were present in less than 10% of the patients with pernicious anaemia investigated in the Blood Clinic in Edinburgh during the past ten years. Accordingly, undue emphasis on such features in textbooks of medicine and in lectures is to be deprecated, since it will hinder rather than help early diagnosis.

It is essential to tell undergraduate and postgraduate students that there are no pathognomonic symptoms or signs which will establish the diagnosis of pernicious anaemia; that tiredness, breathlessness, paraesthesiae, and chronic atrophic glossitis are presenting features which occur frequently in other types of anaemia and in particular in cases of iron-deficiency anaemia; and that diagnosis must be based on accurate blood examination, supplemented sometimes by special methods of investigation.

I am grateful to Dr. J. Richmond, Lecturer in the University of Edinburgh, for his help in collecting and tabulating the data given in the Tables and Figures.

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CLINICAL SIGNIFICANCE OF WEIGHT TRENDS DURING PREGNANCY

BY

A. M. THOMSON, M.B., D.P.H.

AND

W. Z. BILLEWICZ, M.Sc.

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Regular measurement of body weight during pregnancy is clinically valuable. For example, progressive loss of weight helps to confirm the seriousness of vomiting, while a sudden increase of weight may precede the appearance of oedema. It is usually easier to explain a sudden alteration in the rate at which an individual patient gains weight than to explain why overall gains in different patients vary so widely. A few patients gain very little weight, while others gain 50 lb. (22.7 kg.) or more. The impression that many patients who develop pre-eclampsia have high average rates of gain is well substantiated, but there is comparatively little exact numerical information.

The statistical evaluation of weight changes in pregnancy is difficult. A true and complete picture could be obtained only by weighing all pregnant women in a representative community at frequent intervals from conception until delivery, which is practically impossible. It is usual to circumvent the technical difficulties by reporting only on patients fulfilling certain arbitrary criteria. For example, Humphreys (1954) studied 1,000

"normal" mothers, the criteria of normality including such items as first antenatal visit before the 13th week of gestation and last antenatal visit within seven days of delivery; while Scott and Benjamin (1948) selected 360 women weighed regularly at four-weekly intervals from the 16th week. It is difficult to know whether selection on such lines introduces much distortion of results. Some of the difficulties can be avoided by restricting analyses to weight changes during a limited period of pregnancy. Hamlin (1952) has suggested that the 10-week period, 20–30 weeks,* is especially significant in relation to the prevention of eclampsia and pre-eclampsia by weight regulation. Data for this period can be obtained for the majority of cases, since most women come under antenatal care before mid-pregnancy, and few are delivered before the 30th week.

In centres where weight gain is controlled as part of antenatal care it is impossible to obtain a "natural" picture. During the years under review no attempt was made to restrict the amount of weight gained by patients.

Primigravidae are more liable to develop pre-eclampsia and many other complications than multigravidae; therefore studies in which various parities are taken together are not easily interpreted. The analysis which follows relates the "natural" rate of weight gain in primigravidae, especially during the period 20–30 weeks, to the clinical outcome. The findings are discussed in relation to proposals by Hamlin (1952), Dieckmann (1952), and others that severe restriction of the rate of gain helps to prevent eclampsia and pre-eclampsia.

Methods

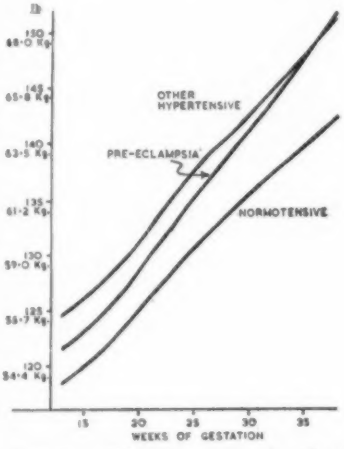
Patients were weighed at the first antenatal visit and again, as a rule, four to six weeks later. Most were then weighed monthly until 28–30 weeks of pregnancy, and more often during the final weeks. Accurate lever balances were used, and patients wore underclothes only. The week of pregnancy within which each weight was taken was accurately calculated in cases where reliable menstrual data were available. Since many patients did not attend during the first trimester, data for the first 13 weeks of pregnancy are too sparse to have any representative value. Trends in late pregnancy are necessarily derived from patients whose pregnancies continued until term or near it.

Records Used and Methods of Analysis

The analysis was restricted to records of legitimate first pregnancies of women resident in the city of Aberdeen and delivered in the Aberdeen Maternity Hospital as booked patients during the six years 1949–54. Multiple pregnancies were excluded. Out of 5,297 records, 1,083 were rejected because either the period of gestation was uncertain or the number of weighings was not large enough to provide the required data with sufficient accuracy. Patients whose records were thus excluded had a slightly lower average age and belonged more often to a lower social class than the remainder. The 4,214 cases analysed have pre-eclampsia, prematurity, and perinatal death rates very similar to those of all hospital-booked primiparae, and it is therefore thought that selection does not invalidate the conclusions drawn from the analyses which follow.

Since the average rate of weight gain is well known to be related to the occurrence of pre-eclampsia, the records were first divided into three clinical groups as follows: (*a*) Cases of pre-eclampsia with albuminuria (6.5% of all cases). (*b*) Cases with other hypertensive complications, mostly mild pre-eclampsia without albuminuria (25.4%). This group includes a few cases diagnosed as essential hypertension. (*c*) Cases without hypertensive complications ("normotensive") (68.1%). The first group corresponds to "severe pre-eclampsia" as defined by Nelson (1955), who has discussed the problems of definition for epidemiological purposes. For the sake of brevity these relatively severe cases will in future be referred to as "pre-eclampsia," without qualification. "Hypertension" connotes a diastolic blood pressure recorded as 90 mm. Hg or above on two or more occasions separated by at least a day, or showing a definite or progressive pattern if the rise occurs in labour.

The problem was to determine whether the weight trends in each clinical group differed according to the stage of pregnancy at which weighing began. This was done by drawing average curves for 11 groups of normotensive patients, in which antenatal care began at different stages. The scatter was so small that it was thought justifiable to pool the results. The scatter in groups of patients with pre-eclampsia and other hypertensive complications was also small.



Average weight-gain curves in three clinical categories of primigravidae.

The Chart shows the average weight curves from the 13th to the 38th week for all cases in each of the three clinical groups. The normotensive patients had the lowest average starting weight (118 lb.; 53.5 kg.), and "other hypertensive" the highest (124 lb.; 56.2 kg.). The average rate of gain, especially in the final trimester, was greatest in pre-eclamptic and least in normotensive cases. These findings justified the separation, *ab initio*, of the three clinical groups.

For each patient, weights in the 13th, 20th, 30th, and 36th weeks were determined, by interpolation if necessary, and the average weekly rates of gain in the three intervening periods calculated. These average weekly rates of gain were the data used for most purposes. The number of cases in each period is different, because some patients had not reported early enough, or were delivered too early or were weighed too irregularly, for inclusion in all three periods.

Results

Average Weight Gains and Variations of Gain

Table I shows the average gain per week in each of the three periods and three clinical groups, together with their standard errors. In normotensive patients the average rate

TABLE I.—*Average Rates of Gains in Three Periods of Pregnancy*

Clinical Group		13–20 Weeks	20–30 Weeks	30–36 Weeks
Pre-eclampsia with albuminuria	No. of cases	166	274	267
	Av. gain/week (lb.)	1·00 (·036)	1·23 (·027)	1·50 (·068)
	(g.)	454 (16)	558 (12)	680 (31)
"Other hypertensive complications"	No. of cases	533	1,072	1,067
	Av. gain/week (lb.)	0·95 (·019)	1·14 (·013)	1·08 (·017)
	(g.)	431 (9)	517 (6)	490 (8)
Normotensive	No. of cases	1,362	2,868	2,833
	Av. gain/week (lb.)	0·92 (·011)	1·03 (·007)	0·87 (·009)
	(g.)	417 (5)	467 (3)	395 (4)

Standard errors are shown in parentheses. In each period the differences between means for clinical groups are statistically significant.

*To simplify notation, periods like 20th–30th or 30th–36th weeks are written as 20–30 and 30–36 weeks respectively. The average time of recording "20th week" weights is, of course, 19.5 weeks; and similarly for other times.

of gain was greater in the period 20–30 weeks than either before or after, whereas in pre-eclampsia the rate of gain tended to increase as pregnancy progressed and was greater at all stages than in the average normotensive case. Further analysis shows that in the period 20–30 weeks the proportion of patients gaining more than 1.6 lb. (726 g.) per week is nearly three times as high in those who eventually develop pre-eclampsia as in those who remain normotensive. This ratio becomes 6 to 1 in the period 30–36 weeks, owing no doubt to oedema adding to the rate of gain in pre-eclampsia. There is, nevertheless, so much overlap that the predictive value of rates of gain is relatively small. The rates of gain are significantly less variable in the period 20–30 weeks than either earlier or later. This is to be expected, since complicating factors such as vomiting and oedema which affect rates of gain are least common in the period 20–30 weeks.

The 20–30 weeks series includes 11 patients who had eclamptic fits. The distribution of weight gains in these is very similar to that for cases of pre-eclampsia.

The total weight gains for the period 13–36 weeks are estimated to be 21.9, 24.6, and 28.3 lb (9.9, 11.2, and 12.8 kg.) for normotensive, "other hypertensive," and pre-eclampsia cases respectively; for all cases together 23.1 lb. (10.5 kg.). To these may be added 2.5 lb. (1.1 kg.) for the first trimester (Chesley, 1944); while the gain from the 36th to the 40th week in normotensive cases was 3.2 lb. (1.5 kg.) and in all cases 4 lb. (1.8 kg.). Thus the gain during the whole of pregnancy is estimated to be 27.6 lb. (12.5 kg.) for normotensive cases alone and 29.6 lb. (13.4 kg.) for all cases in which pregnancy continued until term. A comparable figure for pregnancies complicated by pre-eclampsia would have limited significance, since a relatively high proportion terminate before the 40th week.

Average rates of weight gain do not vary greatly according to the social class, height, or age of patients. Women in the upper social classes and tall women gain slightly more in each period than the others, but the differences are too small to have clinical importance. Older women tend to gain slightly less than those who are young.

The rates of weight gain cannot be related to the usual non-pregnant weight for height (fatness or leanness), since the weight before pregnancy is seldom known. It was therefore decided to study the weight for height at the 20th week in relation to the rate of gain during the period 21–30 weeks. An "obesity index" was calculated for each patient by relating the weight at the 20th week to the median weight at the 20th week for all patients of the same height. The average weight gains did not vary much in relation to the "obesity index." Underweight women tended to gain at slightly lower rates than usual. Since "obesity" was assessed at the 20th week of pregnancy, a high index may, of course, mean simply that the women concerned had put on a relatively great amount of weight during the first half of pregnancy. This may be why women who were moderately overweight at the 20th week had a slightly higher than average rate of gain during the next 10 weeks. On the other hand, women who were unusually heavy at 20 weeks did not gain more than the average.

Clinical Outcome in Relation to Weight Gain

The differences of weight gain in the three main clinical groups are shown in Table I and the Chart. In the analyses which follow, the data for all cases are grouped according to weight gain and the incidence of certain complications in each weight gain category is shown. The weight data used are those for the periods 20–30 and 30–36 weeks; analyses of clinical phenomena in relation to rates of weight gain before the 20th week are of limited value, since the necessary weight data are not available for more than half the cases (Table I). The cases omitted are known to have relatively high rates of prematurity and of perinatal death; they were, for the most part, women who first attended the clinic after mid-pregnancy.

TABLE II.—*Clinical Outcome in Relation to Amount of Weight Gained in the 16-Weeks Period, 20–36 Weeks*

Weight Gained		Pre-eclampsia %	Prematurity* %	Percentage of Prematures* with Pre-eclampsia	Perinatal Mortality per 1,000	No. of Cases
lb.	kg.					
<8	<3·6	2·6	12·1	9	36·0	273
8	3·6	3·3	8·3	9		671
12	5·4	3·1	5·5	16	11·9	1,090
16	7·3	5·7	4·4	25	27·8	1,009
20	9·1	9·2	4·9	35		651
24	10·9	13·5	5·7	47	32·9	296
28+	12·7+	26·0	8·5	66		177

* Birth weight 5½ lb. (2,500 g.) or under.

Table II shows the trends in relation to the amount of weight gained in the 16 weeks period 20–36 weeks. Amongst women who gained 8 lb. (3.6 kg.) or less—that is, at an average rate not exceeding 0.5 lb. (227 g.) a week—the incidence of pre-eclampsia was 2.6%. The incidence increased steadily with increasing rate of weight gain until, in women gaining 28 lb. (12.7 kg.) or more, equal to an average gain of at least 1.75 lb. (794 g.) a week, it was ten times as great (26%). The incidence of prematurity (birth weight 5½ lb. (2,500 g.) or less) shows an opposing trend, falling as the weight gain increases, except that it rises again when the gain becomes very large, owing to the fact that a high proportion of the prematures in the groups with the high weight gain were the result of pre-eclampsia. The high rate of prematurity (defined as low birth weight) associated with low weight gains appears, in the main, to arise from poor foetal growth resulting in the birth of relatively small babies and not from the effects of the well-recognized diseases of pregnancy. But as the rate of weight gain increases, the proportion of prematures associated with pre-eclampsia rises steeply, and in the groups with the highest weight gain the relatively high rate of prematurity is due primarily to premature termination of pregnancy either spontaneously or after induction of labour owing to pre-eclampsia.

The perinatal mortality rates shown in Table II are underestimates, since pregnancies ending much before the 36th week, which have a very high mortality rate, are not included in the data.

Table III shows the incidences of pre-eclampsia, "other hypertensive complications," prematurity, and perinatal death according to the rate of weight gain in the periods 20–30 weeks and 30–36 weeks separately. The grouping of rates of gain is arbitrary, being designed to give reasonably adequate numbers in all categories.

Pre-eclampsia and "other hypertensive complications" both show the same pattern, the highest rates being found when the rate of gain is high in the 30–36 weeks period, irrespective of the rates of gain between 20 and 30 weeks. In the period 20–30 weeks, women gaining more than 1.2 lb. (544 g.) a week had a relatively high expectation of pre-eclampsia, unless the rate of gain subsequently fell below 1 lb. (454 g.) a week in the period 30–36 weeks.

In the case of prematurity, the highest rates are found where the weight gain has been low in the period 20–30 weeks, and especially when the rate of gain has been unusually low or unusually high in the period 30–36 weeks. The rate was only 3%, less than half the average, when the gain was moderate in both periods—that is, 0.8–1.2 lb. (363–544 g.) a week from the 20th to the 30th week, and 0.6–1 lb. (272–454 g.) a week from the 30th to the 36th week.

The advantage of this moderate rate of gain is even more strikingly demonstrated in the perinatal mortality rate. The very low death rate found, 11 per 1,000 births, could be as low as it is by pure chance; however, the statistical probabilities indicate that a rate higher than 20 is unlikely. This low death rate probably reflects the fact that in this weight-gain group the foetus has the best chance of escaping the hazards of pre-eclampsia and of prematurity. In general, the trends of perinatal mortality follow those of prematurity rather than of pre-eclampsia.

TABLE III.—*Incidence of Certain Complications by Rates of Weight Gain in the Periods 20–30 and 30–36 Weeks of Pregnancy*

Gain per Week, 20–30 Weeks		Gains per Week, 30–36 Weeks				
lb.	g.	<0·6 lb. <272 g.	0·6 lb.– 272 g.–	1 lb.– 454 g.–	1·4 lb.+ 635 g.+	All†
Pre-eclampsia (%)						
<0·8	<363	2·3	2·9	5·5	17·5	4·0
0·8–	363–	2·0	2·8	6·2	16·7	5·1
1·2+	544+	3·5	3·0	6·8	18·7	9·7
All ..	..	2·3	2·9	6·4	18·1	6·5
"Other Hypertensive Complications" (%)						
<0·8	<363	17·7	20·2	26·8	36·5	21·0
0·8–	363–	21·5	19·3	26·3	39·1	23·8
1·2+	544+	21·1	25·4	30·5	36·7	30·3
All ..	..	19·7	21·2	28·3	37·3	25·4
Prematurity (%)						
<0·8	<363	10·1	8·8	8·5	7·9	10·1
0·8–	363–	6·9	3·0	5·9	9·4	6·1
1·2+	544+	7·0	3·6	3·9	6·2	5·9
All ..	..	8·4	4·6	5·4	7·2	7·0
*Perinatal Mortality, per 1,000**						
<0·8	<363	39·0	20·5	(–)	(31·7)	30·4
0·8–	363–	34·7	10·9	22·9	31·3	26·0
1·2+	544+	42·3	41·4	22·7	34·1	38·0
All ..	..	37·7	21·5	19·3	33·2	31·3
Numbers of Cases‡						
<0·8	<363	436 (10·5)	341 (8·2)	164 (3·9)	63 (1·5)	1,021† (24·1)
0·8–	363–	404 (9·7)	643 (15·4)	437 (10·5)	192 (4·6)	1,692† (40·2)
1·2+	544+	142 (3·4)	362 (8·7)	485 (11·6)	498 (11·9)	1,501† (35·6)
All ..	..	982 (23·6)	1,346 (32·3)	1,086 (26·1)	753 (18·1)	4,214† (100·0)

* Rates in brackets based on fewer than five deaths.
† Including cases for which adequate 30–36 weeks' weight data were not available, and cases delivered from the 31st to the 36th weeks.
‡ Numbers in brackets are percentages in each "cell."

When analyses of the type shown in Table III are repeated, grouping the weight-gain categories in different ways, the same kind of pattern emerges. The same is true when patients are first subdivided according to weight for height or by "physical grade"—that is, the judgment of the obstetrician at the patient's first antenatal attendance as to her general physique and well-being. Women who were over average weight at 20 weeks had, however, higher rates of pre-eclampsia and lower rates of prematurity than underweight women in nearly all categories.

The last part of Table III shows the numbers involved and their percentage distribution. Forty per cent. of primigravidae were in the moderate weight-gain group for the period 20–30 weeks—that is, gained between 8 and 12 lb. (3.6 and 5.4 kg.). Nearly one-quarter gained less than 8 lb. (3.6 kg.). Only 15% of all cases were in the most favourable group, that which gained 8–12 lb. (3.6–5.4 kg.) from the 20th to the 30th week, and 6–10 lb. (2.7–4.5 kg.) from the 30th to the 36th week.

Discussion

The methods of analysis described were devised primarily to elucidate the clinical significance of various weight-gain patterns, the physiological basis of which will not be discussed. We have shown elsewhere (Thomson and Billewicz, 1955) that the rate of weight gain during pregnancy is positively correlated with the calorie value of the maternal diet.

The weight gains found are consistent with those previously reported. Our estimated average total gain in normal pregnancy, 27.6 lb. (12.5 kg.), and average rate of gain in the period 30–36 weeks, 0.87 lb. (395 g.) a week, are reasonably close to estimates for the total gain and for rate of gain during the last trimester made by Chesley (1944) and by Humphreys (1954).

The relationship between weight gain and incidence of pre-eclampsia follows expectation. As Chesley and others have already noted, the incidence of pre-eclampsia rises as the rate of weight gain increases, but measurement of the rate of gain over a period of time such as 20–30 weeks has little predictive value in the individual case. It has often been suggested that the occurrence of a sudden acceleration in the rate of gain is of more clinical significance than a high average rate of gain. Our records show that this "sign" of incipient oedema or hypertension, while not without value, is not very reliable as a means of prediction.

Primigravidae who develop mild pre-eclampsia have a higher average "starting weight" (observed at the end of the first trimester) than those who develop severe pre-eclampsia or those who remained normotensive. This cannot be wholly explained in terms of age and height differences, and its significance is not clear.

The primigravida aged 30 or over is slightly taller and heavier and has a very slightly lower average rate of weight gain than the younger primigravida. As Nelson (1955) has shown, she also has an increased tendency to develop mild pre-eclampsia, but little or no special liability to severe pre-eclampsia; though when severe pre-eclampsia does supervene the foetal mortality is relatively high. But our more extensive data do not confirm Nelson's suggestion that the tendency to high rates of weight gain with severe pre-eclampsia in primigravidae occurs only under the age of 30. We have no evidence to support the claim of Tompkins, Wiehl, and Mitchell (1955) that women with abnormally low weight gains also have a raised incidence of pre-eclampsia.

It is reasonable to expect some correlation between rates of weight gain and birth weights, since the weight of the foetus accounts for part of the increase of maternal weight. This has been observed, for example, by Kerr (1943) and Beilly and Kurland (1945), and the present data confirm it. In our data, median birth weights rise steadily from 6.7 to 7.5 lb. (3 to 3.4 kg.) as the 20–30 week rates of gain increase from under 0.6 lb. (272 g.) to over 1.8 lb. (816 g.) a week. The high incidence of prematurity (birth weight 5½ lb. (2,500 g.) or less) associated with low maternal weight gains seems to be due more to depression of the foetal growth rate than to curtailment of the length of gestation. In cases of severe pre-eclampsia, usually associated with high rates of weight gain, depression of foetal growth as well as curtailment of pregnancy is usual (Baird, Thomson and Billewicz, 1957); both facts account for the excess of very small prematures in pregnancies where the 20–30 week weight gain was very large.

Where there is no policy of weight restriction during pregnancy, moderate rates of gain are clearly associated with the most favourable clinical experience. Thus, patients who gained 8–12 lb. (3.6–5.4 kg.) from the 20th to the 30th week, and at a slightly lower rate after the 30th week, had pre-eclampsia, prematurity, and perinatal mortality rates only about half the average. Higher rates of gain were associated especially with pre-eclampsia and lower rates especially with prematurity.

It does not follow logically that, if excessively high or low gains are avoided by dietary regulation and other measures, the clinical outcome will be as favourable as in those women who gain the "correct" amounts of weight when left to their own devices. But there is some evidence that restriction of excessive gains is helpful in preventing eclampsia; the evidence that such restriction prevents pre-eclampsia is less satisfactory, perhaps because pre-eclampsia is less easy to define.

Of recent reports along these lines, those by Hamlin (1952, 1953) are the most spectacular. He claimed the abolition of eclampsia (no cases in 6,600 booked patients) and a considerable reduction of severe pre-eclampsia in a large Australian hospital, thanks to an intensive programme of antenatal care, including measures aimed at limiting the amount of weight gained and the admission to hospital of cases of mild pre-eclampsia. Hamlin says that most primiparae who are allowed to gain more than 8 lb. (3.6 kg.) in the 20–30-weeks period will progress inexorably towards pre-eclampsia and eclampsia, but gives no evidence. Hughes (1951), reporting on the same Australian campaign,

merely observes that a gain exceeding 1 lb. (454 g.) a week after the fifth month of pregnancy points to the need for close observation of the patient. Of Aberdeen primiparae who remained normotensive throughout, 73% gained more than 8 lb. (3.6 kg.) in the period 20–30 weeks, compared with 85% of those who developed fairly severe pre-eclampsia. Hamlin's statement is therefore certainly not valid in Aberdeen.

Hamlin (1953) and also Nixon (1955) have republished a "normal" curve of weight during pregnancy derived from Dieckmann, Smitter, and Rynkiewicz (1952); this shows a gain of only 7.7 lb. (3.5 kg.) during the period 20–30 weeks. It is not clear how the patients from whom the curve was derived were selected, nor whether they were required to restrict their weight gains as part of antenatal care. In his monograph on the toxaemia of pregnancy Dieckmann (1952) recommends limiting the weight gain to 200 g. a week during the last 28 weeks of pregnancy, which implies a 20–30 weeks' gain of less than 5 lb. (2.3 kg.). He acknowledges that such targets may be difficult to attain even under ideal conditions: "The fact that we were only able to restrict one-third of the patients to what we consider the maximum gain during an intense nutrition study indicates how difficult it is to restrain calorie intake in these patients."

There is no doubt that, even without a policy of weight regulation, good out-patient antenatal care, backed by adequate hospital facilities, can do much to prevent eclampsia and the more serious consequences of pre-eclampsia. Between 1938–42 and 1954–5 the incidence of eclampsia in primigravidae booked in Aberdeen Maternity Hospital fell from 8 to 2 per 1,000,* and the stillbirth rate in cases of eclampsia and pre-eclampsia from 151 to 25 per 1,000 births. Nelson (1955) has discussed the reasons. We do not know whether progress would have been accelerated if weight regulation had been practised as part of routine antenatal care. The problem now is whether results can be further improved, and especially whether the need for antenatal beds required for the treatment of pre-eclampsia can be reduced by weight regulation.† These questions can be answered only by means of an *ad hoc* trial under controlled conditions.

Preliminary trials have shown that full scientific control is practically impossible to achieve because the measures needed for regulating weight changes inevitably mean that antenatal care is intensified in other respects; again, within one centre, the ideas promulgated at an experimental antenatal clinic soon begin to "infect" staff at the routine clinics from which control cases are drawn. These facts make the value of a policy of weight regulation difficult to assess scientifically. It will be some time before the data of our current trial can be quoted. It seems more easy, by careful dietary supervision, to restrict a rate of gain which has been excessive than to augment a rate of gain which seems unduly low.

The clinical hazards associated with very low "natural" rates of weight gain do not seem to have been systematically studied in the past, though the increased risk of prematurity (especially when the mother is underweight at the beginning of pregnancy) has been noted by Tompkins *et al.* (1955). Women who fail to gain an adequate amount of weight present a problem at least as important as those who gain excessively.

The rule of moderation is probably as sound when applied to weight gains during pregnancy as to many other aspects of existence. As a realistic target, we would suggest gains within the range of ½ to 1½ lb. (340 to 567 g.) a week as being consistent with excellent clinical results. Roughly half of all primigravidae will "naturally" gain weight within this range from the 20th to the 30th week of pregnancy, and it may be that the proportion could be increased by measures practicable at out-patient clinics. The mean rate of gain, 1 lb. (454 g.) a week, is easily remembered, and the patients' progress easily assessed from one clinic visit to the next. There is no real justification for the lower rates that have been widely advocated. Weight restriction is not easy, and the mother who fails to comply with a rigorous schedule may become unnecessarily burdened with guilt; while the one who succeeds, possibly with considerable stress, may be running an increased risk of prematurity.

*The current average incidence of eclampsia in booked cases of all parities, 0.8 per 1,000, is comparable with rates reported from a number of major American hospitals in 1947–9 (Dieckmann, 1952). In the latter, presumably, weight regulation has been practised for many years.

†About 16% of all Aberdeen booked primigravidae are admitted to the antenatal wards for treatment of pre-eclampsia and allied conditions, which account for over 40% of the total antenatal bed-days due to primigravid admissions of all kinds, and absorb an average of about 4 antenatal beds per 1,000 booked primigravidae per annum. The equivalent figures for booked patients of all parities are 12% admitted, 26% of all bed-days, and 3 beds per 1,000 patients per annum.

Summary

An analysis of the weight gains of primigravidae, not subjected to weight regulation, confirmed that the average rate of gain is higher in pre-eclampsia than in normal pregnancy, and that the incidence of pre-eclampsia rises as the rate of weight gain increases. These facts are of little value for predicting pre-eclampsia in the individual case.

The incidence of prematurity (birth weight 5½ lb. (2,500 g.) or less) is highest when weight gains are consistently low, falls as the rate of gain increases, and then rises again with high rates of gain. Pre-eclampsia is an important cause of prematurity in the high but not in the low weight-gain groups.

The most favourable outcome of pregnancy—in terms of pre-eclampsia, prematurity, and perinatal death—is associated with a moderate rate of weight gain, at least throughout the second half of pregnancy. A gain of about 1 lb. (454 g.) a week is suggested as a sound and realistic average to aim at. The more rigorous restriction of weight gain which has been advocated is not justified on present evidence and may be harmful.

We are grateful to Professor Dugald Baird and many of our colleagues for encouragement and criticism, and to the ladies of the records office for hard and accurate work.

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"Infections in Laboratory Animals" is the subject of the fourth volume (1956) of *Collected Papers* published by the Laboratory Animals Bureau. It records the proceedings of a symposium held at the Royal Veterinary College, London, last April, and consists of seven papers on the following subjects: "Epidemiology and Laboratory Mice" (Mr. A. A. Tuffery); "Control of Ectromelia in Mouse Colonies" (Dr. M. H. Salaman); "Control of Infection in Laboratory Cats and Dogs" (Professor W. L. Weipers); "Infections in Laboratory Monkeys" (Dr. A. P. Goffe); "Control of Disease in Rabbits" (Dr. J. Stuart Paterson); "Control of Disease in Laboratory Poultry" (Dr. R. F. Gordon); and "Salmonella in Laboratory Animals" (Dr. Joan Taylor and Mr. J. D. Atkinson). In addition there are the opening remarks and summary of the meeting by the chairman, Professor J. W. Howie. The volume (pp. 68) is obtainable from the Laboratory Animals Bureau, M.R.C. Laboratories, Holly Hill, Hampstead, London, N.W.3, price 7s. 6d.

CALCIUM METABOLISM AND BONE CHANGES IN SARCOIDOSIS

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Although hypercalcaemia is uncommon in sarcoidosis it is important for two reasons. It may cause difficulties in reaching a correct diagnosis, and when persistent leads to complications such as renal failure or nephrocalcinosis. Unless this renal damage is recognized and treated it may be fatal. There is, moreover, evidence that the use of calciferol for the treatment of sarcoidosis in the last decade has increased the risk of hypercalcaemia and of its attendant dangers. The purpose of this paper is to record the frequency of disturbed calcium metabolism in a series of patients with sarcoidosis and to relate it to other features. As this involves a study of the bone lesions in the disease an account of their incidence and forms is also included, from which it is possible to estimate the value of bone radiographs as a diagnostic aid in sarcoidosis.

Clinical Material and Methods

The patients studied belonged to a group of over 160 seen personally during the last few years. The age range was 12 to 65 years, and females preponderated in a ratio of 3:2. About two-thirds of them had widespread pulmonary disease and most of the others had bilateral hilar lymph-node enlargement. Many were referred for investigation after a mass miniature radiograph had shown these abnormalities, and were free from symptoms at the time. About one-quarter of them had a uveitis, one-fifth superficial lymph-node or splenic enlargement, and one-tenth skin lesions. The diagnosis of sarcoidosis was based on a typical chest radiograph and clinical features, supported by negative cultures of sputum and urine for *Mycobacterium tuberculosis*. Confirmation by biopsy was obtained from liver, lymph nodes, skin, or conjunctiva in more than two-thirds of the series.

Radiographs of the hands and feet of 120 of these patients were examined and reported upon by a radiologist. In addition they were reviewed personally at the time of this survey and any doubtful abnormalities were scrutinized together. A control series of radiographs of 101 hands and 14 feet were taken from patients of the same age groups as those with sarcoidosis who attended the casualty department.

Estimations of serum calcium by the method of Trevan and Bainbridge (1926) were made in 86 patients with sarcoidosis (normal range 8.5–11 mg./100 ml.). The serum proteins were estimated by the micro-Kjeldahl method, albumin and globulin being separated by precipitation with sodium sulphate. All patients were examined by the slit-lamp for signs of corneal or conjunctival calcification. Radiographs of the renal tract and function tests were done when there was any reason for thinking that the kidneys were affected.

Bone Radiographs

Bone changes were seen in only 9 of the 120 patients with sarcoidosis (Table I). They were revealed by a coarse reticular pattern in two, typical cystic appearance in two, and intermediate states of medullary and cortical bone replacement in five (Figs. 1 and 2). Confirmation of the diagnosis by liver, skin, or lymph-node biopsy was possible in eight of the nine patients. Estimations of serum calcium in six gave normal results. Local bone pain occurred in three and soft-tissue swelling in two. Five of the nine patients with bone lesions had cutaneous sarcoids, but only eight of the other 111 patients—confirming the relationship between these two forms of sarcoidosis which has long been suspected. The skin lesions did not occur over the areas of bone disease, nor were they of any particular type: all were confirmed by biopsy. Bone disease was not associated with any particular type of pulmonary disease or with other features such as uveitis.

Lesions resembling those of sarcoidosis were not seen in any of the control group of radiographs.

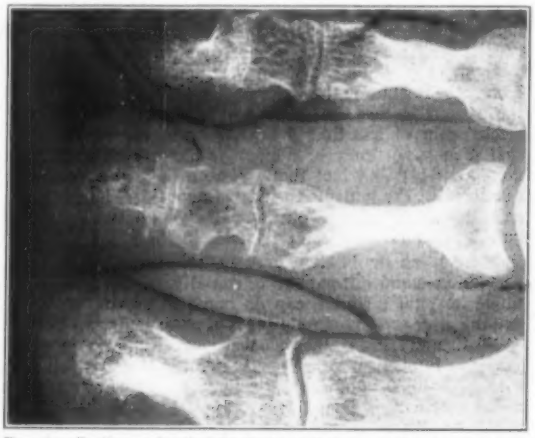

FIG. 1.—Radiograph of right foot of Case A, Table I. Destruction of cortical and medullary bone is seen most obviously in the middle phalanx of the second toe. (By courtesy of Drs. R. J. Cairns and J. D. Craig.)

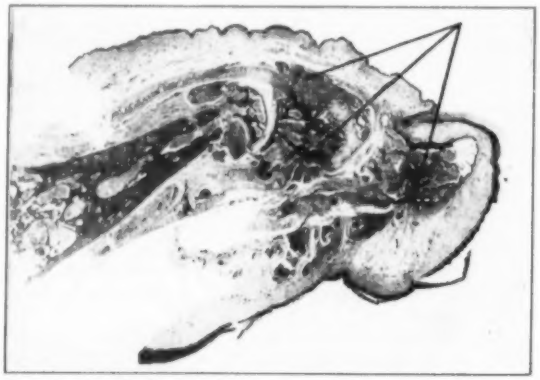

FIG. 2.—Longitudinal section of the second toe of Case A, removed because of pain. Lines point to extensive replacement of bone and surrounding structures by sarcoid tissue. (Haematoxylin and eosin stain. ×2.)

Serum Calcium in Untreated Sarcoidosis

A serum calcium over 11 mg./100 ml. was found in four of 86 patients tested and below 8.5 mg./100 ml. in four others (Table II). No patient had been treated with vitamin D. None of these eight patients had digital bone lesions. There was no relationship between the serum calcium and the serum albumin, but two patients were found to have a parallel change in the level of total globulins. In Case 4 hypercalcaemia was found together with serum globulin of 3.4 g./100 ml. and in Case 5 hypocalcaemia with serum globulin of 0.29 g./100 ml.

One patient only in the series had any symptoms or signs referable to a disturbed calcium metabolism. His case history is given in detail because of the many interesting features.

Case 1

A fit Service man aged 20, with no previous serious illness, was found by a mass radiograph in August, 1952, to have bilateral hilar-node enlargement and basal infiltration. Examination revealed a transient pleural friction rub and crepitations in the base of the left lung. The Mantoux reaction was positive to 100 T.U. *M. tuberculosis* was not isolated from repeated sputum cultures. A liver biopsy confirmed the diagnosis of sarcoidosis.

Two months later he developed enlarged superficial lymph nodes, iritis, and retinal periphlebitis. This responded to a two-months course of systemic cortisone, 100 mg. daily. His general condition remained good and he gained weight while resting in hospital. In August, 1953, proteinuria was noticed and a chest radiograph showed increased pulmonary infiltration. On account of this he was admitted to King's College Hospital in November. Examination then revealed vascularization of the right cornea and circumscribed retinal scars in the left eye. There was generalized lymph-node enlargement, and fine crepitations were heard at the base of the lungs.

Investigations.—Chest *x*-ray examination: bilateral hilar-node enlargement with infiltration at both bases. *X*-ray films of hands and feet: normal. Intravenous pyelography: horse-shoe kidney with two stones in right renal pelvis, also calcified mesenteric node in right iliac fossa. Blood count: normal. E.S.R., 44 mm./hour (Westergren). *M. tuberculosis* not found on repeated sputum and urine culture. Lymph-node biopsy: typical sarcoid follicles. Urine: albumin +, hyaline casts +, white cells +, red cells +, sterile on culture. Urine concentration and dilution test: range of S.G., 1014–1010. Blood urea, 37 mg./100 ml.; standard urea clearance, 40% of normal; serum calcium, 11.6 mg./100 ml.; alkaline phosphatase, 8 K.A. units/100 ml.; plasma phosphorus, 3.3 mg./100 ml.; serum proteins, 7.2 g./100 ml. (albumin 4.2 g., globulin 3 g.).

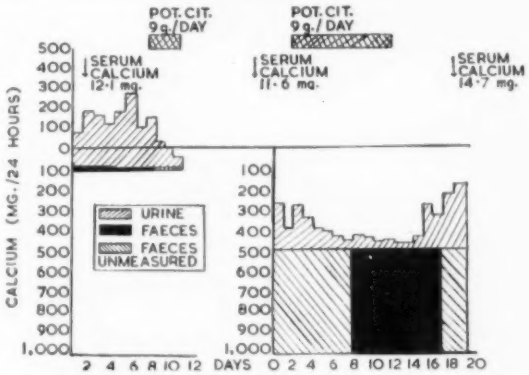

FIG. 3.—Calcium balance in Case 1 on a low and normal calcium intake from December 9–20, 1953, and January 2–21, 1954, respectively. Daily intake is measured downwards from and output upwards towards the zero line. The effect of potassium citrate is seen.

Calcium Balance (Fig. 3).—On an intake of 100 mg. of calcium and 90 I.U. of vitamin D per 24 hours there was a very low calcium excretion in the faeces, but an excretion in the urine which exceeded the intake by about 150 mg. per 24 hours; this was reduced by taking 9 g. potassium

TABLE I.—*Bone Changes in Sarcoidosis* (120 *Patients*)

Case	Age	Sex	Clinical Features	Biopsy Positive	*X*-ray Examination		Serum Calcium (mg./100 ml.)
					Chest	Bone	
A	41	F	Skin lesions, pain in toes	Skin, toe	Normal	Erosions of medulla and cortex of right second toe, proximal and middle phalanges. Erosion of nasal bones (Figs. 1 and 2)	10·8
B	47	F	Skin lesions, aching and swelling of hands and feet, myxoedema	Skin	Hilar nodes +. Diffuse fine infiltration	Cysts of several digits of hands and feet	—
C	40	M	Skin lesions, aching in hands and feet	Skin, liver	Normal	Cortical erosion right second metatarsal head	—
D	43	M	Lupus pernio	Skin, palate	,,	Coarse reticulation with early erosion of heads of several proximal phalanges	8·9
E	40	M	Lymph-node enlargement	Lymph node	Hilar nodes +	Early cystic erosion base middle phalanx right ring-finger	—
F	35	F	Tiredness, dyspnoea, painless swellings of fingers	Subcutaneous tissue	Diffuse coarse mottling	Coarse reticular pattern of several phalanges	9·3
G	47	M	Skin lesions	Skin, liver	Bilateral infiltration, mainly upper zones	Coarse trabeculation and early erosion middle phalanx right ring-finger	9·4
H	42	F	No symptoms or signs	—	Symmetrical coarse reticulation	Typical cyst base of distal phalanx right ring-finger	9·2
I	12	M	Loss of weight and energy. Inguinal nodes	Lymph node	Hilar nodes +	Coarse trabeculation and cortical erosions in proximal phalanges of both third toes	8·8 9·7

TABLE II.—*Abnormal Serum Calcium in Sarcoidosis* (86 *Patients*)

Case	Age, Sex	Clinical Features	Biopsy	*X*-ray Examination		Serum Calcium (mg./100 ml.)	Serum Proteins (g./100 ml.)		
				Chest	Bone		Total	Alb.	Glob.
				High					
1	20 M	Generalized lymph-node enlargement, uveitis, renal stone	Lymph node, liver	Hilar nodes +. Slight lung infilt.	Normal	11·6	7·2	4·2	3·0
2	24 M	Delayed puberty	—	,, ,, ,,	,,	12·3 8·7*	5·92	4·50	1·42
3	23 M	Bilateral iridocyclitis	Liver	Hilar nodes +. Bilateral lung infilt.	,,	11·4	6·54	4·41	2·13
4	22 M	Lymph-node enlargement	Lymph node, liver	,, ,, ,,	,,	11·5	7·7	4·3	3·4
				Low					
5	18 F	Skin lesions, splenic enlargement	Skin	Hilar nodes +. Bilateral lung infilt.	,,	7·8 7·9	4·66 4·7	4·37 3·6	0·29 1·1
6	56	Bilateral iridocyclitis	—	Hilar nodes +	,,	8·4	6·42	4·46	1·96
7	25	Slight chest pain	Liver	Hilar nodes +. Bilateral lung infilt.	,,	8·1	6·84	4·45	2·39
8	36	Skin lesions, uveoparotitis	Skin	Hilar nodes +. Coarse infilt.	,,	8·0	—	—	—

* One month later.

citrate daily. The citrate was given in order to see the effect of alkalizing the urine, as the low calcium diet has an acid ash. On an intake of 983 mg. of calcium and 1,200 I.U. of vitamin D an average of 300 mg. of calcium was retained per 24 hours, with a normal proportion of urinary and faecal excretion; the urinary component was greatly reduced when potassium citrate was given. During this period the serum calcium rose from 11.6 to 14.7 mg./100 ml. The effect of calciferol (10,000 units daily) and cortisone on the calcium balance when on a calcium intake of 718 mg. is shown in Fig. 4. The serum calcium rose from

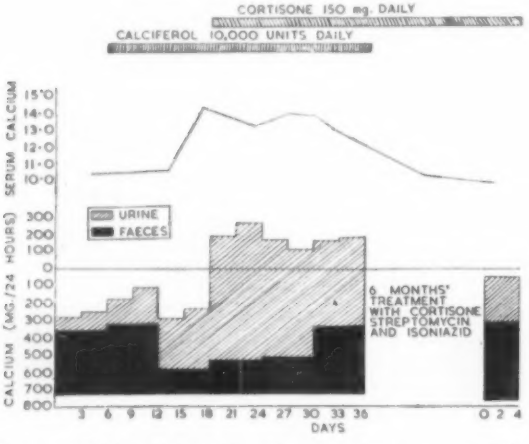

FIG. 4.—Calcium balance in Case 1 during treatment with cortisone from February 20 to March 28, 1954.

10.5 to 14.3 mg. during the 12 days with calciferol alone and there was a fall in the faecal excretion and a steady rise in the urinary excretion. The addition of cortisone, 150 mg. daily, coincided with a still greater urinary loss of calcium due to the calciferol, but this then diminished and there was a steady fall in the level of serum calcium to 10.4 mg. A short balance experiment after treatment with cortisone for six months, calciferol having been discontinued, showed a normal calcium balance and a normal level of serum calcium (10 mg.).

Progress.—During observation in hospital and investigation of the calcium metabolism the patient developed marked photophobia with aching in the eyes. On the exposed area of the bulbar conjunctiva follicles were found containing minute chalky granules, together with an early band-shaped opacity in each cornea. This appearance was thought to be associated with the hypercalcaemia, as the serum calcium at this time was 14.7 mg./100 ml. The follicles and band-shaped opacities resolved rapidly when the calcium intake was reduced, and had disappeared within six weeks, leaving only small amorphous deposits in the position of the follicles.

Treatment.—He was given a course of streptomycin sulphate, 1 g. intramuscularly daily, together with isoniazid, 100 mg. b.d., for three months. There was little response in either the clinical or the radiographic features. Cortisone, 150 mg. daily by mouth, was then added and produced a rapid reduction in the size of the superficial lymph nodes, a clearing of the pulmonary infiltration, and a shrinkage of the hilar nodes. The effect on calcium metabolism is shown in Fig. 4. This treatment was continued for three months, during which he returned to work. The dose of cortisone was then reduced to 100 mg. daily, and the streptomycin to 1 g. twice weekly. The chest radiograph and superficial lymph nodes remained normal, there were no signs of active uveitis, and the serum calcium was within normal limits. All treatment was stopped after one year. The patient remained well, and one year later there had been no relapse. The serum calcium was still normal, and kidney function had improved; there was no albuminuria, and the standard urea clearance was 76% of normal.

Disturbed Calcium Metabolism Due to Treatment with Calciferol

No patients were treated with calciferol, but four were seen who showed signs of poisoning after having this drug elsewhere. They are not included in Table II. The case histories of three of them are given.

Case 9

A 51-year-old woman had complained of tiredness and lack of energy for three years. For two years she had noticed a skin lesion on the side of the neck and enlarged cervical lymph nodes which had increased in size six months previously. For 18 months she had had slight dyspnoea on exertion, with a cough productive of a few blobs of white sputum daily. In November, 1954, biopsy of a cervical lymph node had revealed sarcoid follicles. A chest radiograph showed extensive disease, thought to be tuberculous, although the sputum was negative for *M. tuberculosis*. She was treated by rest at home and given 2 pints (1,140 ml.) of milk a day, but there was no real change. Between February 7 and March 8, 1955, she was given 5 ampoules by mouth, each containing 600,000 units of calciferol. On March 11 headache and vomiting began, and the possibility of cerebral tumour was entertained until the serum calcium was found to be 15.4 mg./100 ml. and the blood urea 128 mg./100 ml. There was no frequency of micturition, and no pain or haematuria. The headaches and vomiting were temporarily relieved by chlorpromazine and compound codeine tablets.

When examined at King's College Hospital she displayed a slow mentality, perhaps due to the chlorpromazine. She was anaemic, but the skin was bronzed. In the eyes a few chalky fragments were visible on the exposed area of bulbar conjunctiva. The retinal vessels showed early hypertensive change. There were discretely enlarged cervical, right axillary, and epitrochlear lymph nodes and the spleen was just palpable. Bronchial breathing was heard over the right dorsal lobe, but there were no adventitious sounds. The cardiovascular system was normal apart from a blood pressure of 170/110.

Investigations.—Chest *x*-ray examination: bilateral coarse nodulation, becoming confluent in the upper lobes with upward retraction of the hila by fibrosis. Hands and feet: mild arthritic changes only. Kidneys: no calcification seen. Blood count: haemoglobin, 66%; white cells, 4,300, with normal differential count. E.S.R. (Westergren): 60 mm. hour. Sputum (×6) and E.M.U.: no *M. tuberculosis* on culture. Urine: sterile, albumin 1+, pus cells +++, occasional hyaline and granular casts. Blood urea 55 mg./100 ml.; standard urea clearance, 32% normal. Range of specific gravity, 1006–1012. Serum proteins, 7.27 g./100 ml. (albumin 3.69 g., globulin 3.58 g.). Serum calcium, 12.7 mg./100 ml. Phosphorus 4 mg./100 ml. Alkaline phosphatase, 8 K.A. units/100 ml. E.C.G.: normal. Mantoux: positive to 100 T.U.

A calcium balance was undertaken three months after the last dose of calciferol. On a fixed intake of 615 mg. of calcium per 24 hours there was an excessive excretion of calcium in the urine: an average of 597 mg. in the urine and 336 mg./24 hours in the faeces during six days. The effect of 100 mg. of cortisone daily was to lower the blood calcium to normal, with little change in the proportion of calcium excreted in the urine and faeces during the 12 days in which these were measured.

Progress.—She improved steadily while taking cortisone. The nausea and headache ceased; she became more alert and energetic and resumed an active life. By November, 1955, she looked and felt very fit except for some dyspnoea on exertion due to her old pulmonary lesions, which were unaltered. Her serum calcium has remained within normal limits since June, 1955.

Case 10

A 53-year-old woman in 1940 noticed blurred vision due to uveitis. She developed parotitis and pulmonary sarcoidosis and later multiple skin lesions, and enlarged spleen and lymph nodes. During the next 10 years she became breathless from increasing pulmonary fibrosis. In 1950 she was treated with calciferol, 50,000 units, by mouth daily for nine days, without benefit, but this had to be discontinued on account of vomiting and weakness due to hypercalcaemia. The serum calcium rose to 12 mg./100 ml. In 1954 she had renal colic due to stones, which were later removed. Her blood pressure was 150/95 before treatment with calciferol, but steadily rose afterwards, and reached 235/135, with persistent albumin in the urine. It seems probable that all these complications were caused by the temporary hypercalcaemia. She took her own life in 1955; necropsy confirmed fibrosing sarcoidosis. There was extensive scarring of the kidneys from arteriolar disease, scattered calcification of the renal tubules and interstitial tissue but no sarcoid follicles, and a calculus in the right renal pelvis.

Case 11

A 45-year-old woman noticed enlarged lymph nodes in the neck and axilla in 1946 which were subsequently shown at biopsy to be due to sarcoidosis. Since 1949, during the summer months, she had developed lassitude, vomiting, and constipation of such severity as to make her cease work. In June, 1950, there was an episode of misty vision associated with a painful right eye. In November, 1955, she was given 50,000 units of calciferol daily by mouth for four weeks; but this caused severe lassitude, vomiting, and constipation. She was then referred to King's College Hospital for further investigation. Enlarged cervical, epitrochlear, axillary, and inguinal nodes were found, and an early corneal band-shaped opacity. The blood pressure was 180/90, but there were no abnormalities in the chest, heart, or abdomen.

Investigations.—Radiographs of the chest, skeleton, and kidneys were normal. A barium meal showed only delayed gastric emptying. The Mantoux test was positive to 100 T.U. E.S.R. (Westergren) 45 mm./hour. Cultures of gastric washings and urines were sterile. Serum calcium, 15.2 mg./100 ml. (repeated); phosphorus, 3.2 mg.; urea 65 mg. Total serum proteins, 8 g./100 ml. with increase of globulin on electrophoresis.

Progress.—She was treated with a low-calcium diet and cortisone, 150 mg. daily. Within a month the serum calcium had returned to normal limits (10.8 mg.) and her symptoms had disappeared. Her treatment was interrupted by an attack of acute appendicitis, which, however, gave the opportunity to confirm the diagnosis of sarcoidosis by biopsy of a mesenteric node. Treatment with cortisone has continued on a maintenance dose of 150 mg. daily; her lymph nodes have returned to normal size and gastrointestinal symptoms have disappeared.

Corneal Band-shaped Opacities

Although examination for these opacities was undertaken as a routine, they were found in only three patients. Case 1 was the most obvious. In another patient with uveitis and hilar-node enlargement, corneal calcification was seen, but unfortunately there was no histological proof of sarcoidosis and the serum calcium was not estimated. In the third patient (Case 12) there was circumstantial evidence of transient hypercalcaemia, but the serum calcium was not estimated at the time.

Case 12.—A 65-year-old diabetic woman developed uveitis in 1949 followed by parotitis and skin lesions, which on biopsy were shown to be sarcoids. One year later she developed neuritis, nausea, and vomiting; there was a trace of albumin in the urine, and the blood urea was 140 mg./100 ml. Band-shaped opacities developed, but the serum calcium was not estimated until two years later, when the nausea and vomiting had stopped and the blood urea had returned to 65 mg./100 ml. There was persistent albuminuria. It is probable that both the kidney damage and the corneal opacities were caused by a transient hypercalcaemia.

Discussion

Bone Lesions

The earliest descriptions of the radiographic appearance of bone sarcoid were by Kienböck (1902) and Kreibich (1904), although Jüngling (1919) first described the histological changes. The frequency of bone involvement was found to be 9 in 55 cases by Holt and Owens (1949) and 19 in 100 cases by Longcope and Freiman (1952). Bone disease was found less often in the present series—only nine times in 120 patients. The true frequency of bone involvement may be much higher than any of these reports suggest, as the epithelioid cell follicles of sarcoidosis have been seen at biopsy or necropsy even when the radiograph has been normal (Schaumann, 1926). Also the earliest radiographic changes—a stippled medullary pattern from diffuse lacunar absorption—may be so indefinite that a firm diagnosis cannot be made, especially when the process affects many phalanges.

The explanation for the lower frequency in this series compared with others may be that most of the patients had predominantly intrathoracic sarcoidosis, and that there were only 13 examples of skin sarcoids, of which five showed digital bone disease. The relation between skin and bone sarcoidosis is well known (Holt and Owens, 1949), and it is because so many of the early reports of sarcoidosis were of skin lesions that bone changes were thought to be so frequent. In the last two decades pulmonary forms of the disease have been recognized to be the most common, so that bone sarcoid is seen relatively less frequently.

In the nine patients of this series the diagnosis of sarcoidosis had already been made from the clinical and radiographic features, supported by biopsy in eight. The finding of bone lesions in Cases F and H (Table I) was valuable support for the diagnosis, but their absence would not have changed this. Hence it is thought that radiographs of the hands and feet give little help in the diagnosis of sarcoidosis, and are wasteful as a routine procedure.

The most common type of radiographic change is a coarse reticulation of the shaft of the bone due to follicle formation along the cortical blood vessels, as seen in six of the nine cases. This and a stippled medullary pattern from diffuse lacunar absorption are the earliest changes. The classical punched-out areas in the medulla occurred in two cases, with less definite areas of bone replacement in four others. Thinning and expansion of the cortex, sometimes even with pathological fractures, have been reported due to the enlarging granuloma, but no examples were seen in this series. When the disease remits spontaneously there is seldom complete resolution of the bone lesions; a "cyst" of fibrous tissue may remain indefinitely. Bone sarcoid has been described in practically every bone in the body, but it has an overwhelming predilection for the middle and distal phalanges of the hands and feet. The reason is unknown.

In the differential diagnosis of bone sarcoid many diseases have to be considered. Both rheumatoid arthritis and gout have quite distinct clinical features. Here pain and swelling of the joints predominate, and the radiographic changes of osteoporosis or bony erosions are usually most pronounced at the articular ends of the bones, although in the arthropathy of psoriasis these may spread to involve the shaft as well. Enchondromata usually expand the cortex and are homogeneously translucent. Resembling these are the small degenerative cysts which occasionally occur as an incidental finding in the carpals and digits. Tuberculous dactylitis, a very rare condition in adults, causes the bone to appear distended and provokes a periosteal reaction; later destructive changes may occur accompanied by sinuses. Hyperparathyroidism should seldom be mistaken for sarcoidosis, as here there is decalcification affecting the whole skeleton,

with fibrous cysts in a few bones. Sometimes it may not be possible to separate xanthofibroma and tuberous sclerosis of the digits except by features of these diseases elsewhere. The most common error is to diagnose digital sarcoidosis too frequently through failure to appreciate the range of normal bone architecture. Areas of radiolucency in the metacarpal heads are especially apt to be interpreted falsely, as are the coarsening of the bone structure with increasing age and with osteoarthritis. Features which help in the diagnosis of sarcoidosis are the lack of joint involvement and periosteal reaction, and the usual absence of pain.

No relationship has been found between demonstrable bone disease and hypercalcaemia either in the past (Holt and Owens, 1949) or in the present series (Table I). This is not surprising, as other localized diseases of bone, such as osteomyelitis or tumours, likewise do not upset calcium metabolism. Bone sarcoid must be regarded as an oddity which seldom causes symptoms or demands treatment.

Hypercalcaemia

The first recognition of hypercalcaemia in sarcoidosis was by Harrell and Fisher (1939). Isolated reports of nephrocalcinosis and renal calculi had appeared (Salvesen, 1935), but their relationship to hypercalcaemia was not appreciated until 1941 (van Creveld). Estimates of the frequency of hypercalcaemia have varied from 11 in 44 patients (Longcope and Freiman, 1952) to 4 in 86 of the present series. Harrell and Fisher (1939) reported hypercalcaemia in 6 of their 11 patients, but in one patient the serum calcium was only 10.6 mg./100 ml., and, in another, hypercalcaemia developed only after intensive treatment with cod-liver oil. The explanation for the lower frequency in the present series compared with those of previous workers may be that many of the patients had disease affecting the hilar nodes or lungs alone and none was given vitamin D. Many of the reported cases had widespread disease, and no mention was made of whether vitamin D had been given as treatment. Hypercalcaemia in patients not receiving vitamin D occurs so infrequently in sarcoidosis that estimation of the serum calcium routinely is unnecessary. It should be done if there are symptoms of hypercalcaemia such as thirst, polyuria, tiredness, muscular weakness, and vomiting, if ectopic calcification is found, or if renal colic or albuminuria occurs, pointing to nephrolithiasis or calcinosis.

The explanation for the hypocalcaemia in four patients (Table II) is obscure, but merits further investigation. Case 5 was of particular interest in that there was an associated hypoglobulinaemia despite extensive sarcoidosis.

The cause of hypercalcaemia remains obscure. It bears no relation to a high serum protein (Harrell and Fisher, 1939; and Table II); in any case, protein disturbances affect only the serum globulin, which has little calcium-binding power (Schmidt and Greenberg, 1935; Gutman and Gutman, 1937). Also the hypercalciuria is evidence that increased calcium in the blood is largely of the ionizable fraction. Hypercalcaemia is not due to parathyroid stimulation, as there is no hypophosphataemia or generalized osteoporosis. In several cases normal parathyroid glands have been removed (Albright and Reifenstein, 1948; Klatskin and Gordon, 1953; Davidson *et al.*, 1954; Anderson *et al.*, 1954). One case has been recorded where hyperparathyroidism simulated sarcoidosis by showing diffuse pulmonary reticulation (Salmon and Meynell, 1951).

Hypercalcaemia is not due to widespread bone sarcoid, as there is seldom radiographic evidence of this, and in the nine cases (Table I) with known bone lesions there was no upset of calcium metabolism. Furthermore, balance studies do not support this hypothesis. It is not due to renal sarcoidosis, as there are many examples of hypercalcaemia where biopsy or necropsy has failed to show epithelioid cell follicles (Dent *et al.*, 1953; Davidson *et al.*, 1954; Correa, 1954; Case 10), and in those cases where renal sarcoidosis has occurred it is not extensive enough to cause impaired function (Longcope and Freiman, 1952). It may be due to a primary metabolic disorder, such as excessive sensitivity to vitamin D as suggested by Anderson *et al.* (1954). Case 1 showed on the calcium balance an excessive absorption of calcium similar to that seen in their cases. This patient's metabolism also reverted to normal during cortisone treatment, a feature observed by Shulman *et al.* (1952), Lovelock and Stone (1953), Phillips (1953), Dent *et al.* (1953), Lane (1954), Citron (1954, 1955), and Anderson *et al.* (1954).

Further support for the hypothesis of vitamin-D sensitivity comes from the observations on Case 1 and of others that treatment with this drug even in small doses or with ultra-violet light may cause hypercalcaemia (Scadding, 1950; Cantwell, 1954; Letman, 1954; Anderson *et al.*, 1954). The recurrent symptoms of hypercalcaemia in Case 11 before calciferol was given all occurred during the summer months and were especially severe during the sunny summer of 1955. This suggests that the hypercalcaemia was provoked by ultra-violet light. Moreover, the clinical as well as the biochemical features of hypercalcaemia in sarcoidosis are in every way typical of hypervitaminosis D. Sensitivity to vitamin D is also thought to be the cause of infantile hypercalcaemia (Bonham Carter *et al.*, 1955; Schlesinger *et al.*, 1956), and there is some evidence that cortisone helps to reverse this abnormality (Creery and Neill, 1954).

The dangerous effects of hypercalcaemia, whether spontaneous or provoked by vitamin D, are primarily on the kidney, where irreversible damage may be done by nephrocalcinosis and renal stones (Cases 9 and 10). Impairment of function may be so severe that a fatal uraemia ensues (Cantwell, 1954; Correa, 1954; Davidson *et al.*, 1954). Hypercalcaemia may also cause band-shaped corneal opacities (Walsh and Howard, 1947; Cogan *et al.*, 1948; Cases 1, 9, and 11), and calcification in tissues, such as the blood vessels, lungs, subcutaneous tissue, and joint capsules. In addition to these potential dangers, there is considerable doubt about the efficiency of calciferol in the treatment of sarcoidosis. In the only recorded controlled trial of calciferol (Nelson, 1949) the frequency of remissions was the same in the treated and untreated groups. For these reasons the use of calciferol for the treatment of sarcoidosis should be discontinued.

When hypercalcaemia is encountered, a diet low in calcium and vitamin D may be effective. Cortisone has been shown to have some antagonistic action to vitamin D and is effective in reducing hypercalcaemia in sarcoidosis. It should be used when there is evidence of renal damage and when dietary measures prove ineffective.

Summary

Radiographs of the hands and feet have been examined from 120 patients with sarcoidosis: bone lesions were found in only nine. Such radiographs are thus of little value in diagnosis. The common association of cutaneous sarcoids with bone disease was confirmed (five out of the nine patients). No examples of disturbed calcium metabolism were seen in those with bone disease.

Estimations of serum calcium in 86 untreated patients showed hypercalcaemia in only four. Hypocalcaemia occurred in four. The effects of hypercalcaemia are described, with special reference to kidney damage. Examples of hypercalcaemia following the treatment of sarcoidosis with calciferol are given and its dangers emphasized.

Clinical and biochemical studies support the hypothesis that hypercalcaemia in sarcoidosis is due to excessive sensitivity to vitamin D. Control of this complication may be achieved by a diet low in calcium and vitamin D, although cortisone is sometimes necessary.

I thank Dr. A. M. Rackow, Dr. C. E. Dent, and Professor C. H. Gray for their help, and Mr. A. H. Dawson, senior

laboratory technician, for the biochemical estimations. I am also grateful to Dr. Clifford Hoyle for his constant encouragement and advice.

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ANAESTHESIA FOR AORTIC RECONSTRUCTION*

BY

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Reconstruction of the thoracic and abdominal aorta calls for an anaesthetic technique appropriate to other operations in the region of these structures. There are, however, certain features peculiar to this branch of surgery which demand some special thought from the anaesthetist. Apart from the technical problems involved in maintaining (often for many hours) an even state of anaesthesia, combined with the profound degree of muscular relaxation necessitated by the surgical approach, there are other, and vital, matters concerning blood and respiratory chemistry, fluid and blood replacement, and the control of the haemodynamic disturbances of the surgical procedure. The nature of the operation may necessitate interruption of the circulation to vital organs for long periods, and in such cases the operation can be conducted safely only with the aid of induced hypothermia; this technique will itself impose some problems of anaesthetic management.

The anaesthetic techniques described below have been followed in 71 of the cases of aortic occlusion or aneurysm undergoing operation by members of the surgical unit of St. Mary's Hospital, London, under the direction of Professor Charles Rob. The anaesthetic procedure was conducted by three members of the hospital consultant staff, and their assistants. The 71 cases concerned are briefly summarized in Table I.

*Abstracted from a paper read before the Section of Anaesthetics at the Annual Meeting of the British Medical Association, Brighton, 1956.

TABLE I

	Requiring Hypothermia	Not Requiring Hypothermia
Aneurysm	5	37
Thrombosis	6	22
Coarctation	1	0
Total	12	59

TABLE II.—*Fatal Cases*

Requiring Hypothermia		Not Requiring Hypothermia	
Aneurysm:		Aneurysm:	
Haemorrhage	1	Haemorrhage	3
Suprarenal failure	1	Myocardial infarction	2
Myocardial infarction	1	Paralytic ileus and pulmonary sepsis	1
		Undecided	1
Thrombosis	0	Haemorrhage	1
Coarctation	0	Coronary thrombosis	1
Total	3		9

The operative mortality (deaths occurring in the first 24 hours of the operative period) was 12 out of 71 (16.9%) (Table II).

Anaesthesia as a contributory cause of death could be implicated for certain in one case (pulmonary sepsis following aspiration of vomitus during induction of anaesthesia for reopening abdomen 12 hours after operation for aortic aneurysm. Ileus not diagnosed preoperatively). One other case (listed as "undecided") was a possible "anaesthetic death." In the light of later experience it was thought that respiratory acidosis might have been a contributory factor (see last two cases in second column).

Type of Patient

Although, in the main, the patients likely to be encountered in surgery of the aorta may be described as being "in the prime of life," they are by no means in the prime of physical condition. With some few exceptions (such as the rare traumatic case, and some cases of aortic coarctation) they have reached middle or late middle age, and are suffering from severe arterial disease. Atherosclerosis is not likely to be confined to the portion of the aorta requiring surgery; coronary, cerebral, and renal vessels are likely to share in the general disease. Often there is hypertension, which may be of severe degree. There may have been past episodes of cardiac infarction or cerebral thrombosis. Such patients tend to be "old beyond their years," physically flabby, and often obese.

This is our somewhat unpromising material, and to subject such patients to major surgery, with the attendant hazards of blood loss and traumatic shock, under general anaesthesia (possibly maintained for as long as 12 hours), without the most careful pre-operative assessment and preparation, would be to court almost certain disaster. Only in the case of true emergency (such as leading aneurysm or haemorrhage from other causes) is it justifiable to omit the full pre-operative routine which is described below. The period of assessment and preparation may precede the operation by 7 to 10 days.

Pre-operative Investigations

Aortography.—In all cases the site of the lesion is determined by an aortogram, usually performed under local analgesia, assisted by intravenous pethidine. Only in exceptionally difficult cases, or with unusually apprehensive patients, will a general anaesthetic be necessary; since complete apnoea at the time of the exposure and the prone position are demanded, this will require tracheal intubation

and controlled respiration. The choice of the subsequent anaesthetic technique will depend on the site of the lesion as revealed by the aortogram. Should the lesion be estimated to lie 2 cm. or less below the level of the renal arteries, clamping of the aorta above this level and interruption of the renal circulation must be envisaged. In lesions of the thoracic aorta the proximal clamp will occlude some part of the blood supply to the spinal cord via the spinal branches of the posterior intercostal arteries. Such cases will call for induced hypothermia.

In addition to a complete physical examination the following routine investigations are carried out on all cases: complete blood count; estimation of haemoglobin, serum proteins, blood sugar, and blood urea; and a complete picture of the plasma electrolytes. Renal and respiratory function tests are made. Wherever electrolyte imbalance is found, every endeavour is made to restore normality, and not until stability seems assured is surgery contemplated. Certain cases require additional investigation and preparation. Of particular importance are those showing respiratory insufficiency; an important example of this group is that of chronic emphysema, which most anaesthetists will recognize as a troublesome problem in major surgery. In all such cases the blood oxygen content, *p*H, and plasma carbon dioxide content are determined, and operation is deferred until physiotherapy, together with antibiotic treatment of residual infection, has resulted in maximal improvement in the patient's vital capacity. The problem of respiratory acidosis is of great importance in the management of anaesthesia for aortic surgery—and, indeed, for most other types of thoracic and abdominal surgery—and is referred to below.

On the night before operation water diuresis is induced by the slow intravenous infusion of 1–2 litres of 5% glucose in water. This is believed to give some measure of protection from subsequent renal failure, particularly when surgical interruption of the renal circulation is anticipated (Wynn, unpublished observation).

It will be seen that cases for aortic reconstruction (or disobliteration) fall into two main groups: (1) those with lesions situated more than 2 cm. below the renal arteries, and (2) those with lesions at, above, or close to the renal arteries or involving the thoracic aorta—that is, cases not requiring induced hypothermia (group 1), and those in which induced hypothermia is obligatory (group 2). For convenience these two groups are considered separately with regard to management, the simpler (non-hypothermic) group being taken first.

Anaesthetic Management of Group 1 Cases

In contrast with those of the second group, group 1 cases will suffer little disturbance of normal physiology, except that at certain stages in the operation severe variations in blood pressure are to be expected and considerable loss of blood may be inevitable. As in all abdominal surgery, muscular relaxation of a high degree is demanded, and, since the operation is likely to be lengthy, the anaesthetic agents must be of minimal toxicity. Our choice at St. Mary's Hospital is nitrous oxide and oxygen, preceded by thiopentone, and supplemented by pethidine. Curare is used to provide the necessary relaxation. Endotracheal intubation is invariably employed, and respiration is controlled manually throughout the operation, with carbon-dioxide absorption on the "to-and-fro" principle. We are careful to avoid small gas-flows, with their potential danger of underventilation.

The administration of parenteral fluids, both in replacement therapy and as vehicles for drugs required in the course of operation, has received some special attention from the team in our metabolic unit. This matter is discussed below. For group 1 cases we prefer to use an isotonic dextrose–saline solution (dextrose 4.3%, saline 0.18%), which is usually administered through a "polythene" intravenous cannula. The solution can be exchanged for whole blood when necessary. An intra-arterial blood transfusion can be set up at very short notice. Since the lower limbs are not available for this purpose (on account of surgical occlusion of the aorta), a transfusion set, kept externally sterile, is retained for the use of the surgeon as need arises. We do not favour the use of the radial or other proximal limb arteries for transfusion purposes, because of the risk of spasm and ischaemia. In most cases the aorta, proximal to the clamps, is the vessel of choice. The necessary transfusion pressure is obtained by suspending the blood-bottle from the theatre gallery at a height of about 10 ft. (3 metres), an extension of the transfusion tube allowing for this distance. Blood pressure and pulse rate are recorded at 10-minute intervals, and electrocardiographic tracings are made when required.

Recently we have come to appreciate the great importance of maintaining a normal blood *p*H, and, in order to detect and check developing respiratory acidosis, estimations of arterial blood *p*H and total carbon dioxide are made at frequent intervals, or whenever there is clinical suspicion of rising blood pCO_2 (rising systolic and diastolic blood pressure, sweating, tachycardia). Further estimations are made at the conclusion of operation, when spontaneous respiration is re-established.

Blood Replacement.—So far as is possible, blood replacement is adjusted to blood loss. The suction-bottle is calibrated in millilitres, and all swabs and packs are weighed before and after use on a sterile balance, blood loss being calculated on a weight-volume coefficient. Since no wet packs are used, an estimate accurate to ±10% is possible. The most critical period of the operation is when the distal aortic clamp is released. Close co-operation between surgeon and anaesthetist ensures that the latter has ample warning and can take the necessary action to avert a dangerous fall in blood pressure. Provided that the intravenous blood

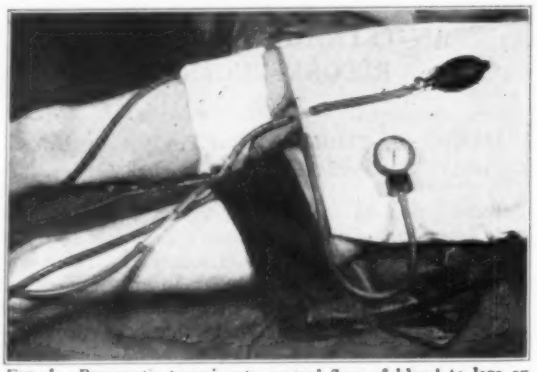

FIG. 1.—Pneumatic tourniquets control flow of blood to legs on release of clamps.

transfusion is capable of a rapid increase in rate of flow (500 ml. in five minutes) at least five minutes before release of the clamp, it is seldom necessary to transfuse intra-arterially. To prevent too rapid a loss of blood into the lower limbs we use pneumatic tourniquets, which can be gradually deflated, and, if necessary, reinflated to check dangerous falls in blood pressure (Fig. 1). Unless unusually severe leakage at the anastomosis occurs on removal of the clamps, blood pressure should be controlled and stabilized within 5–10 minutes.

Anaesthetic Management of Group 2 Cases

In the surgical unit of St. Mary's Hospital we have found the method of *surface-cooling* both simple and effective. We aim at reducing the body temperature to between 26 and 27° C. (78.8 and 80.6° F.), and require about one and a half hours to achieve this degree of hypothermia. The procedure is as follows.

One hour prior to cooling—that is, two and a half hours before the planned time of operation—the patient is premedicated with pethidine, 100 mg., scopolamine, 1/150 gr.

(0.43 mg.), and chlorpromazine, 25–50 mg. intramuscularly. My own practice is to give chlorpromazine, 25 mg., some days before operation, and to observe the effect. Should tachycardia or marked hypotension result I omit the chlorpromazine from the premedication entirely. If, on the other hand, the drug is well tolerated, I give the larger or the smaller dose, according to the patient's fitness and physique. We have not been impressed with the "lytic cocktail" or other methods of so-called "chemical hibernation"; indeed, we feel that such techniques may add further hazards to the operation, tending to aggravate hypotension and to produce excessive thermo-lability.

FIG. 2.—Set-up of anaesthetic and other apparatus during induction of hypothermia. Note ice-bags. *Left foreground:* Control for cutting in thermocouple leads for direct temperature readings. *Left background:* Electrocardiogram. (The apparatus attached to right lower leg is for measuring calf blood flow.) *Right foreground:* Anaesthetic apparatus and sphygmomanometer

Induction of anaesthesia is with thiopentone, and tracheal intubation is performed with the aid of a short-acting muscle-relaxant (succinylcholine).

Maintenance of anaesthesia is by nitrous oxide and oxygen with manually controlled respiration. Increments of pethidine are added intravenously as required. Before cooling is started, tubocurarine chloride, 20–30 mg., is administered. This not only facilitates the control of respiration in a light plane of anaesthesia, but is essential in preventing shivering, with the attendant risk of ventricular fibrillation.

Cooling (conducted on the operating table) is begun by placing ice-bags in close contact with the patient's exposed neck, thorax, abdomen, flanks, thighs, and legs, covered overall by a wet cotton sheet, from which evaporation is assisted by electric fans. The theatre temperature is kept as low as possible (40–60° F.; 3.3–15.5° C.). Body temperature is constantly recorded by thermocouples placed in the upper and lower oesophagus and rectum. Pulse, blood pressure, and electrocardiographic tracings are taken at short intervals, the latter being particularly valuable in giving warning of ventricular arrhythmias (Fig. 2).

Since Wynn (1954) has shown that glucose ceases to be metabolized at a body temperature below 31° C. (87.8° F.), the only parenteral infusion used, apart from blood, is half normal saline, to which is added such drugs as are required in the course of operation. All active cooling is stopped when the body temperature has reached about 28° C. (82.4° F.), after which, in a cool theatre, it will continue to fall until it stabilizes at between 26 and 27.5° C. (78.8 and 81.5° F.). Too rapid a fall in temperature can be checked by removing some of the ice-bags, stopping the fans, and recovering exposed parts of the body with blankets. Operation is started as soon as the require basic temperature has been reached. At this stage it is usually necessary to give a further small dose of curare and/or pethidine.

Provided that the cooling process has proceeded smoothly, the patient, although presenting a somewhat alarmingly lifeless appearance, should by this time have suffered little or no fall in blood pressure. The pulse rate will have fallen considerably (50–60 a minute).

Cases of this group require especially careful handling at the time when the distal aortic clamp is released, for, although vasoconstriction is active as a result of the hypothermia, reflex hyperaemia will still occur in the lower limbs, in response to the restored circulation (Fig. 3). Unless this is adequately controlled by the tourniquets a hypotensive crisis will be precipitated, and this is likely to prove more difficult to treat than in the non-hypothermic cases. Infusion of noradrenaline (1/500,000) will be of great help in such cases, provided that there is not the additional complication of uncompensated blood loss.

A danger associated with massive blood transfusion is inherent in the quantity of sodium citrate which may be infused. Like glucose, the citrate ions of sodium citrate are not metabolized in the hypothermic state, and may reach a concentration high enough to be toxic to the myocardium (Bunker *et al.*, 1955). Furthermore, stored blood has a high potassium-ion concentration which can cause cardiac arrest. In all cases it is advisable that only freshly donated blood be used and that an adequate supply be available at the time of operation. (Aneurysm cases may require as much as 3–4 litres; thrombosis cases, somewhat less.) If the quantity of citrated blood is necessarily heavy (above 4 litres) we advise the addition of calcium gluconate, 0.5 g. to each half-litre.

Post-operative Points

At the conclusion of the operation the anaesthetist must be satisfied upon the following points: (1) blood loss has been restored (verified gravimetrically and volumetrically); (2) blood pressure is stable at a safe level (not less than 100 mm. Hg systolic, with or without noradrenaline); (3) the neuromuscular block has been fully reversed by neostigmine; (4) central respiratory depression has been abolished (this may require nalorphine); (5) the blood *p*H and pCO_2 are normal and stable; and (6) rewarming of the hypothermic patient is proceeding at the rate of 1–1.5° C. an hour, but no faster.

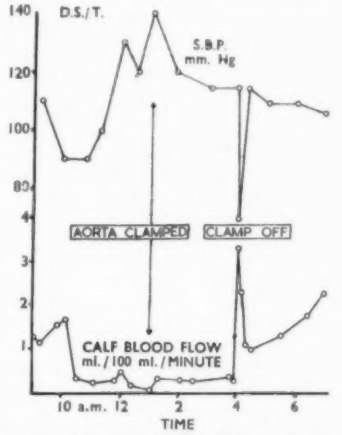

FIG. 3.—Reflex hyperaemia of lower limbs following release of aortic clamp.

These last two points deserve some further amplification, and the fifth point—that is, the matter of blood *p*H—will be taken first, since this applies to both hypothermic and non-hypothermic cases, and is closely related to the problems

of persistent neuromuscular block and central respiratory depression. In a proportion of cases, Wynn (1956, personal communication) and the metabolic team of the surgical unit at St. Mary's Hospital have found that there is a tendency to recurrence of a neuromuscular block which has been previously reversed by neostigmine at some time during the recovery period. It is possible that in the hypothermic patient curare may persist in some depot inaccessible to the action of neostigmine ; or, in those cases where the renal circulation has been interrupted, there could be delayed excretion of curare. Undoubtedly there are other factors as yet not fully understood. Scurr (1954) has already drawn attention to the apparent synergism between carbon dioxide and the neuromuscular blocking agents, and it would seem that in certain circumstances a vicious circle could become established (Fig. 4).

To break this circle the full respiratory efficiency needs to be restored, and treatment must be at the appropriate level. Thus, if reversal of central respiratory depression plus reversal of neuromuscular block (nalorphine plus neostigmine) fails to restore the *status quo*, artificial ventilation aimed at elimination of carbon dioxide must be instituted without delay, and must be continued until the *p*H and pCO_2 return to normal and show no tendency to further change. Reintubation of the patient and connexion to a respiratory pump for an hour or more has sometimes proved necessary. *Respiratory acidosis must never be allowed to develop.* The longer treatment is delayed the more difficult will it be to reverse the process.

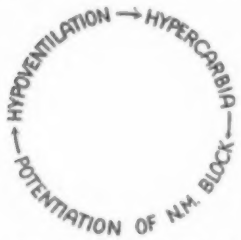

FIG. 4.—Vicious circle of carbon dioxide retention.

Illustrative Case

A somewhat obese plethoric man aged 44 had a recent history of claudication of buttocks and legs. Aortogram (under general anaesthesia) showed occlusion of abdominal aorta immediately below renal arteries, with well-marked collateral circulation. Operation was begun at 9 a.m. under induced hypothermic and thiopentone–nitrous-oxide–oxygen–pethidine–curare anaesthesia with manually controlled respiration. Duration of anaesthesia was about eight hours. Surgical procedure (disobliteration and graft) required clamping of aorta above renal vessels for about two hours. Operation was completed at 6 p.m.

Post-operative Course.—Patient regained consciousness and spoke rationally about 30 minutes after return to the ward. Although respiration was spontaneous on removal of endotracheal tube, there was marked "tracheal tug," which was not abolished by neostigmine, 2.5 mg., repeated after 20 minutes. Oxygen was administered by means of a plastic facepiece at the rate of approximately 8 litres a minute, a good colour being maintained. Rewarming proceeded normally ; no shivering. Three hours later (9 p.m.) respiration became shallow and soon ceased, although the colour up to this time (with oxygen) had seemed satisfactory. Patient appeared deeply unconscious. Artificial respiration with oxygen by means of a bag and facepiece (later replaced by cuffed tube) was immediately begun. Blood samples were obtained for *p*H, HCO_3, and pCO_2, which revealed very gross respiratory acidosis (see Fig. 5).

Four hours later (1 a.m.) the patient still appeared deeply comatose ; *p*H was now rising, and HCO_3 and pCO_2 falling slightly. At this stage a Waters CO_2 absorber was placed in circuit. Much heat was generated, requiring change of canister after 20 minutes. Artificial respiration continued until 6 a.m. (a further five hours), when consciousness and spontaneous respiration returned. Blood samples now showed an almost complete return to normal, except the *p*H, which remained a little low (7.35) for about a further hour. Thereafter the patient made an uninterrupted recovery.

Comment.—An interesting feature of this case was revealed some time later. The patient, who was himself a medical man, was able to recall in detail many of the events which took place when he appeared to be deeply comatose. This would seem to be a case of respiratory acidosis simulating complete neuromuscular block (Scurr, 1954).

Rewarming of the hypothermic patient requires the most careful vigilance on the part of medical and nursing staff. If

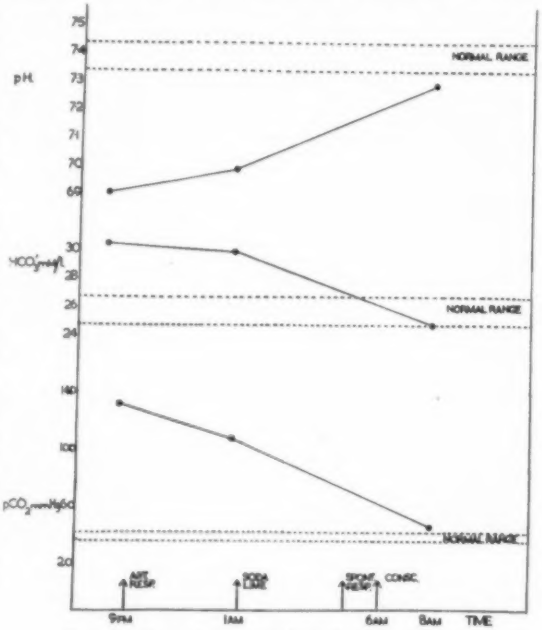

FIG. 5.—Case of severe carbon dioxide retention.

rewarming proceeds too rapidly, vasodilatation will result in a severe fall in blood pressure ; if too slowly, shivering and shock may be produced. We believe that a safe average rate of rewarming lies between 1 and 1.5° C. an hour. Heat-loss is prevented by blanketing in preference to the application of outside sources of heat, such as electric cradles. Should the body temperature rise too rapidly, and result in a fall in blood pressure, it may be necessary to reapply tourniquets to the limb from time to time, whilst removing some or all of the blankets.

Conclusion

It should be observed that although the operative death rate in cases of aortic reconstruction might appear to be high in comparison with that encountered in the general run of major abdominal and thoraco-abdominal surgery, due appreciation must be given to the extreme severity of the operations performed on patients almost invariably in the "poor-risk" group. As in all comparatively new branches of surgery, improvement in this respect may be expected to follow future improvements in technique, both surgical and anaesthetic. A decrease in the incidence of operative shock and blood loss is already beginning to reflect a steady diminution in total operating-time, whilst experience has taught us to avoid many of the earlier hazards of anaesthesia.

The paramount importance of team-work in the management of these cases must be stressed. Without the close co-operation of the many special departments (electrocardiographic, metabolic, biochemical, to mention only a few of those whose services we are fortunate in having at our disposal) the anaesthetic and operative risk in major aortic surgery would be formidable indeed.

Summary

The pre-anaesthetic preparation, anaesthetic technique, and post-anaesthetic management of cases of aortic reconstruction are described.

Blood loss, blood and fluid replacement, and the control of blood pressure are discussed.

The technique of induced hypothermia by the method of surface cooling is described, and some relevant problems are considered.

The importance of maintaining a normal blood chemistry, with particular reference to the blood *p*H and pCO_2, is stressed.

I thank Professor Charles Rob for giving me access to case notes and statistics of the St. Mary's Hospital Surgical Unit; Dr. Victor Wynn for much valuable assistance and for supplying the graph (Fig. 5) from his personal notes; and Dr. P. N. Cardew, of the St. Mary's Hospital photographic department, for the illustrations and diagrams

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CANICOLA FEVER IN MAN THROUGH CONTACT WITH INFECTED PIGS

BY

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Leptospiral infections in man resulting from contact with infected pigs have been reported from different parts of the world but have not previously been recorded in Great Britain. Thus the benign human leptospiroses known as "swineherd's disease" and "seven-day fever of Queensland" have followed contact with pigs infected with *Leptospira pomona* (syn. *L. suis*) and *L. mitis* (syn. *L. hyos*) respectively, while van Thiel (1948) quotes two published cases of Weil's disease where it seemed likely that the patient had contracted the disease through slaughtering pigs infected with *L. icterohaemorrhagiae*.

Neither *L. pomona* nor *L. mitis* has so far been isolated from man or pig in this country, but occurrences of *L. icterohaemorrhagiae* infection in swine in two rat-infested piggeries in the south-east of Scotland have been reported by Nisbet (1951).

One other type of leptospira—namely, *L. canicola*—has been isolated from swine. Williams *et al.* (1953) found during the investigation of an extensive outbreak of human canicola fever in a rural community in South Georgia that dogs, cows, and swine showed evidence of infection with *L. canicola*. All the human cases had bathed in the water of a creek to which animals had access, and, although the original source of infection remained obscure, it was the first record of *L. canicola* infection in animals other than dogs.

Previously it had been generally accepted that dogs were the only natural carriers of *L. canicola* (van Thiel, 1948) and that infection in man resulted directly or indirectly from contact with these animals. The disease in the dog varies in severity, but, whatever the degree of illness, the infection usually leads to leptospiruria, which may persist for many months if recovery occurs, thereby providing a source of contamination for other dogs and for man. While the number of known cases of human canicola fever has been steadily increasing, its true incidence is difficult to assess, since it is a disease which must very often escape diagnosis. In some instances of human disease the history would seem to leave little doubt that infection was transmitted from a dog, but others have been recorded where no apparent connexion between patient and dog could be established (Broom, 1951) and where an alternative source of infection seemed probable. It may be that pigs are more frequently infected with *L. canicola* than is commonly supposed, and, if so, the question arises whether they may not act as reservoirs of infection to persons who feed and handle them. Investigations into a number of obscure cases of human canicola fever which occurred between 1950 and 1955 among piggery workers in and around the City of Edinburgh gave rise to a series of interesting results which point to the probable role of pigs in the transmission of canicola infection to man. These form the basis of the present communication.

Laboratory Methods

Agglutination-lysis tests were used for serological diagnoses. The methods of setting up the tests and interpreting the results were those developed by the staff of the Institute of Tropical Hygiene in Amsterdam, and are described in detail by Wolff (1954). Live cultures of leptospires were used, and the sera were diluted from 1 in 10 to 1 in 30,000. Titres of 1 in 100 and over are regarded as indicating past or present leptospiral infections. A few titres as low as 1 in 10 to 1 in 30 have been recorded, but they are to be treated with reserve since their significance is doubtful.

The isolation of leptospires from the organs of infected animals at necropsy was attempted by grinding small pieces of tissue in Korthof's medium in a Waring blender and inoculating tubes of medium with three or four drops of the emulsion so produced. Latterly, however, we were more successful in obtaining positive cultures by inoculating duplicate tubes of Korthof's or Stuart's medium with small pieces of kidney tissue punched out with a Pasteur pipette, after the surface had been seared with a red-hot scalpel blade (cf. Wolff, 1954). The tubes were incubated at 28° C. and examined at weekly intervals up to six weeks before being discarded as negative.

In addition to culture, hamsters approximately 3 weeks old were inoculated intraperitoneally with 0.5 ml. of tissue emulsions or with 0.5 ml. of centrifuged urine deposit suspended in 1 ml. of Korthof's medium.

Microscopical examinations of cultures, urine, and heart blood from experimental animals were made with dark-ground illumination using a 2-mm. objective.

Clinical Observations

The first case to be investigated occurred in November, 1954, when a man employed on a piggery (Farm A) was admitted to hospital with a feverish illness of eight days' duration characterized by severe frontal headache. Blood taken from the patient agglutinated *L. canicola* to a significantly high titre. Although, on inquiry, no history of recent illness was forthcoming, blood from four out of five other persons living and working on the farm gave positive agglutination findings. The results of these tests and other relevant features are shown in Table I.

There were three dogs on the farm, and, to determine whether they might have been responsible for the infection, specimens of blood and urine were obtained. Dark-ground examination of the urine failed to reveal leptospires. Two of the sera agglutinated *L. canicola* to titres of 1 in 30 and 1 in

TABLE I.—*Details of Personnel Living and Working at Farm A*

	Age	No. of Years Working with Pigs	Remarks	Serum Titre of Agglutination Against	
				L. canicola	*L. icterohaemorrhagiae*
Mr. A. ..	23	4 months	Case of canicola fever	(1) 1/30,000 (2) 1/30,000	1/1,000 1/3,000
Mr. W. D.	60	45 years	Owner of piggery (no significant previous history)	1/1,000	1/300
Mrs. W. D.	50	Intermittently over a number of years	Wife of owner (no significant previous history)	1/10,000	1/300
Mr. J. D. ..	30	15 years	Son (no significant previous history)	1/3,000	1/300
Mrs. J. D.	30	No association with pigs	Daughter-in-law	Negative	Negative
Mr. B. ..	40	20 years	Piggery worker (no significant previous history)	1/3,000	"

100, while none of them agglutinated *L. icterohaemorrhagiae*. These low agglutination titres and the absence of leptospires in the urine did not point to the dogs as the direct source of infection, and, as the only person in the piggery whose blood failed to agglutinate leptospires was also the only one of the six persons concerned who had no contact with pigs, it occurred to one of us (J. N.) that the pigs might be harbouring the organisms and serving as a reservoir of infection. Consequently, blood samples were taken at random from 75 of the animals and submitted for serological examination. The results are shown in Table II.

TABLE II.—*Results of Leptospira Agglutination Tests with Pig Sera from Farm A*

	Total Tested	Titres of Agglutination							
		Neg.	1/10	1/30	1/100	1/300	1/1,000	1/3,000	1/10,000
L. canicola	75	17	1	11	24	7	8	4	3

Thus evidence of infection with *L. canicola* based on positive serological findings was present in 46 of the 75 pigs tested (61%), while in 12 others a low degree of agglutination was obtained. Although, in the cases of the positive sera, cross-reactions occurred with *L. icterohaemorrhagiae* the titres never exceeded those with *L. canicola* and were usually much less. Twelve sera were also tested against *L. pomona* and *L. mitis* with negative results.

The interesting results obtained at Farm A were a stimulus to further study and, as a first step, inquiries were directed to another piggery (Farm B), in connexion with which a confirmed case of canicola fever had occurred two months previously. Specimens of blood were obtained from this man and his nine fellow workers, and also from 98 pigs taken at random on the farm. The results of leptospira agglutination tests, with other details, are given in Tables III and IV.

Table III shows that in four out of nine persons working at the piggery there was serological evidence of previous infection with *L. canicola*. Apart from the original patient, none of these workers, in spite of careful interrogation, gave a history of an illness suggestive of canicola fever.

It will be seen from Table IV that 40% of the pigs tested had antibodies to *L. canicola* present in their sera to a significant extent.

Inquiries were now extended to 10 other piggeries, and specimens of blood were obtained from 31 workers. Serological tests in 21 were negative, but the other 10 were positive and their agglutination titres with other relevant information are set out in Table V.

It should be mentioned that at three of the piggeries all eight workers examined were free from evidence of infection. No pigs were examined on these farms. The 10 cases with positive sera were among the 23 employees at the remaining seven farms. It is also of interest that at one of the latter farms 12 pigs out of 31 tested were found to have sera positive to *L. canicola*.

Summarizing the results shown in Tables I to V, it appears that of a total of 47 blood specimens taken from persons employed or living at 12 pig farms, 19 (40%) were found to contain antibodies to *L. canicola* in amounts sufficient to signify a past infection with that organism. Five of the persons concerned had had previous illnesses diagnosed at the time on clinical and serological grounds as canicola fever, while an additional five gave histories of undiagnosed illnesses, the symptoms of which, in retrospect, suggested canicola fever. As regards the pigs, 86 out of 173 (50%) at Farms A and B showed evidence of infection with

TABLE III.—*Details of Personnel Living and Working at Farm B*

	Age	No. of Years Working with Pigs	Remarks	Serum Titre of Agglutination Against	
				L. canicola	*L. icterohaemorrhagiae*
Mr. F. ..	17	½	Case of canicola fever	(1) 1/3,000 (2) 1/10,000	1/300 1/1,000
Mr. W. N.	50	40	No significant symptoms	1/1,000	Negative
Mr. I. N.	17	1	" "	1/30	"
Mr. M. ..	33	6	" "	1/3,000	—
Mr. S. ..	26	Intermittently for several years	" "	Negative	—
Mr. J. ..	50	1½	" "	"	—
Mr. R. ..	50	10	" "	"	—
Mr. W. ..	40	20	" "	"	—
Mr. McN.	17	1	" "	1/3,000	1/30
Mr. T. ..	30	1	" "	Negative	Negative

TABLE IV.—*Results of Leptospira Agglutination by Pig Sera from Farm B*

	Total Tested	Titres of Agglutination						
		Neg.	1/30	1/100	1/300	1/1,000	1/3,000	1/10,000
L. canicola ..	98	54	4	21	11	5	1	2

TABLE V.—*Details of 10 Piggery Workers Whose Sera Agglutinated Leptospirae*

Name	Age	No. of Years Working with Pigs	Remarks	Titres of Agglutination Against		
				L. canicola	*L. icterohaemorrhagiae*	*L. pomona*
Mr. D. McD.	42	Many	History suggestive of canicola fever 7 years ago	1/10,000	1/300	Negative
Mr. W. McD.	47	"	History of illness diagnosed as ?tuberculous meningitis 7 years ago	1/1,000	1/30	"
Mr. M. S. ..	20	3	No record of illness	1/300	Negative	"
Mr. E. N. ..	40	17	History of severe influenza 4 years ago	1/300	1/10	"
Mr. McC. ..	18	2	History of severe influenza 6 months ago	1/300		
Mr. J. S. ..	32	3	Severe "influenza" 2 months previously	1/100		
Mr. D. R. ..	26	10	Canicola fever diagnosed 5 years ago	1/3,000	1/30	
Mr. R. R. ..	23	8	No record of illness	1/1,000	Negative	
Mr. K. ..	57	5	Canicola fever diagnosed 5 years ago	1/1,000	1/30	
Mr. C. ..	33	Intermittently	Canicola fever diagnosed December, 1955	1/3,000	1/100	

L. canicola to a significant degree. None of these animals revealed noticeable signs or symptoms of disease.

These findings strongly suggested the probability that infection had been transmitted from pig to man, but so far it had not been possible to isolate the leptospira from either pigs or man. Only one of the five human cases of confirmed canicola fever was ill during the course of the present investigation, and in his case blood cultures, dark-ground examination of the urine, and animal inoculation gave negative results, probably because he was not brought under notice at a sufficiently early stage of the disease. Specimens of urine from the bladders of a large number of pigs on Farm A showed no leptospires on dark-ground microscopy, and we failed to isolate the organism by inoculating hamsters with kidney tissue from "non-thriving" pigs with high antibody titres for *L. canicola*. It should be noted, however, that there was in the piggery at the time a concurrent infection of *Pasteurella septica* which killed the hamsters rapidly and contaminated the culture media inoculated at necropsy.

Because of the failure to demonstrate leptospires by these methods, it was decided to carry out experimental work to determine whether pigs could be artificially infected with *L. canicola* and whether leptospires could then be isolated from the urine of these pigs.

Experimental Investigations

1. Artificial Infection of Pigs with L. canicola

Six pigs aged 2–3 months whose sera failed to agglutinate *L. canicola* and *L. icterohaemorrhagiae* were inoculated with a culture of *L. canicola* (strain Aldgate) kindly supplied by Dr. J. C. Broom, of the Wellcome Laboratories of Tropical Medicine. This strain is highly virulent (a hamster inoculated with 0.3 ml. of the culture died on the fifth day). The pigs were inoculated by the following routes: (1) Subcutaneously through the soft skin of the groin (0.5 ml.). (2) By scarification of the skin behind the ear, one drop of culture being placed on the scarified area, covered with cotton-wool, and held firmly in place with medicated elastic adhesive bandage. (3) Intranasally by rubbing the inside of each nostril with a swab saturated in the culture. (4) Routes 1, 2, and 3 combined. (5) By mouth: 1 ml. of the culture was introduced into the back of the throat by means of a syringe. (6) Control.

Evidence of Disease Resulting from Inoculations.—Rectal temperatures of the pigs recorded before the experiment and each day afterwards showed no significant rise. No apparent symptoms of disease developed and the pigs continued to gain in weight.

Serology.—Ten days after inoculation, and periodically thereafter until the pigs were killed, blood was withdrawn from the ear veins and agglutination tests were carried out with the sera against *L. canicola*. The results are shown in Table VI. These results show that a marked serological

TABLE VI

Pig No.	Method of Inoculation	Titres of Agglutination of *L. canicola*			
		Before Inoculation	No. of Days After Inoculation		
			10	28	40
1	Subcutaneous ..	Negative	1/30,000	*	
2	Scarification ..	,,	1/10,000	1/10,000	—
3	Intranasal ..	,,	Negative	Negative	Negative
4	Methods 1, 2, and 3	,,	1/10,000	*	
5	By mouth	,,	Negative	1/300	1/3,000
6	Control	,,	,,	Negative	Negative

* Pigs 1 and 4 were killed on the 18th and the 12th day respectively.

response followed inoculation of the culture by all routes except the intranasal one. Subcutaneous inoculation and inoculation through the scarified skin resulted in strongly positive agglutinating sera within 10 days. On the other hand, antibody production in the pig inoculated by mouth was delayed and titre had reached only 1 in 100 by the 28th day, continuing to increase to 1 in 3,000 by the 40th day. It is possible in this case that the actual infection may have been acquired through contact with the pigs already infected by the other methods, although it is noteworthy that pigs 3 and 6 failed to show any evidence of infection 47 days after the beginning of the experiment. The result in the pig infected through scarified skin (No. 2) is particularly interesting, since it not only indicates that the serological response must have resulted from invasion of the tissues by the leptospires but also that it is possible for natural infection to follow leptospiral contamination of wounds, so often inflicted when pigs fight with one another.

Attempts to recover infecting organisms were unsuccessful. Dark-ground examination of blood from the infected pigs taken 10 days after inoculation and urine specimens taken periodically thereafter failed to show leptospires.

Pig 4 was killed on the 12th day, pig 1 on the 18th day, and pigs 2 and 5 on the 40th day after inoculation. At necropsy no lesions were seen in any of the organs, and we were unable to recover leptospires from the kidney and liver of these four pigs either by cultural methods or by inoculation of hamsters.

2. Introduction of Non-infected Pigs into the Infected Piggery

In order to observe the effect of introducing non-infected pigs into an infected piggery the following investigation was carried out at Farm A.

Two pens of 20 pigs were chosen for this study. The pigs in the first pen—pen 1—had been introduced into it direct from the local market three weeks previously; those in the second pen—pen 2—one week previously. Both pens had housed pigs which on serological evidence were infected with leptospires, but after these had been removed for slaughter the pens had been given their customary cleaning by hosing and left vacant for 24 hours prior to the introduction of the fresh pigs. Three pigs from each pen were chosen, and blood specimens from the ear veins of the six were found to contain no leptospiral antibodies. Subsequent specimens of blood were taken from the six at intervals and tested against *L. canicola* and *L. icterohaemorrhagiae*. The results are shown in Table VII.

TABLE VII

Pig No.		Length of Time in Piggery							
		1 Week		3 Weeks		5 Weeks		8 Weeks	
		L. can.	*L. ictero.*	*L. can.*	*L. ictero.*	*L. can.*	*L. ictero.*	*L. can.*	*L. ictero.*
Pen 1	1	—	—	Neg.	Neg.	Neg.	Neg.	1/1,000	1/300
	2	—	—	,,	,,	,,	,,	1/10,000	1/1,000
	3	—	—	,,	,,	,,	,,	1/10,000	1/1,000
,, 2	4	Neg.	Neg.	1/300	1/100	1/300	1/100	1/300	1/100
	5	,,	,,	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
	6	,,	,,	,,	,,	,,	,,	,,	,,

From the serological results shown in this Table it appears that the three pigs in pen 1 became infected within six to eight weeks of their introduction into the piggery. In pen 2 the blood of one of the pigs agglutinated leptospires weakly to a titre of 1 in 300 after three weeks, but the titre failed to rise during the subsequent weeks and its significance is therefore doubtful. The other two pigs continued to be serologically negative.

Isolation of L. canicola from Urine.—A specimen of urine taken from the floor of pen 1 during the eighth week was examined by dark-ground microscopy and found to contain numerous leptospires (approximately one per field of uncentrifuged urine). The following day a pooled specimen of urine collected in a sterile long-handled pan from 12 pigs in this pen was examined, and again numerous active leptospires were seen (up to four per field). Separate specimens were then obtained in sterile containers from individual pigs in the pen and five out of six were found to be positive. On the other hand, eight specimens of urine taken from individual pigs in pen 2 were examined by dark-ground microscopy but no leptospires were seen. This accords with the negative serological findings for this pen.

A pooled specimen of urine from the pigs in pen 1 was inoculated into two hamsters: one of these died on the sixth and the other on the eighth day after inoculation. At necropsy, apart from some congestion of the blood vessels of the peritoneum, there were no obvious lesions. Dark-ground examination of heart blood failed to show leptospires, but six drops inoculated into Stuart's medium produced growth after 14 days' incubation. The culture was sent to Dr. Broom at the Wellcome Research Laboratories, and was identified as a strain of *L. canicola*.

3. Experimental Infection of Pigs with Infected Urine

Two of the six pigs used in experiment 1—namely, the one inoculated intranasally and the control animal—continued to show no serological evidence of infection. No leptospiral antibodies were present in either of these animals 47 days after the beginning of experiment 1. The following day they were inoculated with infected urine collected from 10 pigs in Farm A (pen 1). (The presence of leptospires was confirmed by dark-ground microscopy.) Pig 3 was inoculated subcutaneously with 3 ml. of untreated urine, while in the case of pig 6 a piece of cotton-wool soaked in urine was placed on an artificially scarified area behind the ear and held in place with medicated elastic adhesive bandage.

Symptoms of Disease Following Inoculation with Infected Urine.—Rectal temperatures were taken before the inoculations were made and daily thereafter. In both pigs a rise of several degrees was noted, from 102.5 to 106° F. (39.2 to 41.1° C.) on the sixth day in the case of pig 3, and from 102.8 to 104.6° F. (39.3 to 40.3° C.) in pig 6 on the 10th day. No other obvious symptoms developed. Blood cultures from a subcutaneous vein on the fifth day failed to produce a growth of leptospires. Blood-agar plates inoculated with the blood and incubated aerobically and anaerobically remained sterile, showing absence of concurrent septicaemia. Dark-ground examinations of urine taken on the 15th, 19th, and 20th days failed to reveal leptospires. Agglutination tests carried out with blood taken at intervals resulted in the titres with *L. canicola* and *L. icterohaemorrhagiae* shown in

TABLE VIII

Pig No.	Inoculated	Days After Inoculation					
		5		11		21	
		L. can.	*L. ictero.*	*L. can.*	*L. ictero.*	*L. can.*	*L. ictero.*
3	Subcutaneous	Neg.	Neg.	1/3,000	1/30	1/30,000	1/300
6	By scarification ..	..	..	1/10,000	1/1,000	1/30,000	1/1,000

Table VIII. It will be seen that inoculation of the infected urine by both routes was followed by a high antibody level by the 11th day.

Necropsy.—The two pigs were killed 22 days after inoculation. The post-mortem examination revealed no abnormalities. Bottles of Stuart's medium were inoculated with kidney and liver tissue from both pigs. Leptospires grew in one of the bottles inoculated with kidney from pig 6. The growth was slight after 12 days, but by the 18th day numerous leptospires were present. One of two hamsters inoculated with emulsified kidney from pig 6 died 14 days later, showing epistaxis and a post-mortem picture characteristic of a leptospiral infection with pronounced haemorrhages in the lungs. A blood culture from this animal gave a fair growth of leptospires by the 7th day and cultures of the kidney were positive one week later. A few drops of the heart blood introduced intraperitoneally into the second hamster resulted in its death 10 days later. A blood culture from this second animal resulted in growth of leptospires within one week. We failed to isolate leptospires from pig 3 either by culture or by animal inoculation, although two out of four hamsters inoculated with emulsified kidney died in 11 days with haemorrhagic lesions characteristic of leptospiral infection.

Discussion

The evidence submitted above has indicated that 19 out of 47 (40%) piggery workers engaged in 12 different farms in the environs of Edinburgh had been infected at some time with *L. canicola*. It seems probable that the infection resulted through contact with infected pigs, since in one farm 77% of the pigs tested, and in another 44%, had serum antibodies to *L. canicola* and the organism was shown to be excreted at times in large numbers in the urine. This high incidence of infection in humans is particularly striking, since in view of the small number of cases which result from man's contact with infected dogs (the only source of infection previously known to exist for man) it was thought that *L. canicola* had a low infectivity to man. When one takes into consideration the large number of dog-owners in the country and the fact that 25–40% of dogs show serological evidence of infection (Stuart, 1946; Broom and Macintyre, 1948) it is surprising that cases of human canicola fever do not occur more often. Broom (1951) found that persons most liable to become infected were those who had nursed a sick dog and cleaned up its dejects. On the other hand, McIntyre and Seiler (1953), investigating in Edinburgh the incidence of canicola fever among owners of dogs known to be infected with *L. canicola*, found that of 99 persons who had been in contact with sick animals and including 45 who were responsible for removal of the dejects, none were serologically positive to *L. canicola*.

It may be that in the case of piggery workers the conditions under which these men work predispose them to infection. It is known that they frequently suffer from open cuts and wounds in their hands which are apt to become contaminated when cleaning out the pens. In Farm A, where the rate of infection both in humans and in pigs was most striking, conditions in the pens may have been conducive to maintaining the infection. This piggery usually houses a herd of 400 pigs, which are all swill fed. No breeding is done and replacements are made as required from the local markets at ages of 2–3 months. Little bedding is used and the pens are hosed daily, so that the floors, other than the sleeping quarters, are rarely dry and often very wet. The pigs are crowded together from 20–30 in a pen, a practice adopted to maintain a high temperature in the piggery. It seems possible that the leptospires may remain viable for a fairly long time on the moisture-laden floors. It is not known how the pigs were originally infected, but it seems likely that the farm dogs which have access to the piggery may have introduced it and, once established in the herd, the infection has passed from pig to pig through infected urine contaminating skin abrasions or the mucous membranes of the mouth and throat.

While canicola fever in man is not as a rule a killing disease, two fatal cases have been reported (Weetch *et al.*, 1949; Wolff *et al.*, 1951). Furthermore, clinical infection with *L. canicola* gives rise to a sharp illness with meningeal symptoms alarming to the patient and his relatives and incapacitating the victim for some weeks. It is clear, therefore, that all possible steps should be taken to prevent the disease.

Up to the present the main emphasis has been placed on the possibility of spread of infection from dogs, but the results described in this paper indicate that infected pigs are a more important source. This fact should be made widely known to pig owners and their employees so that they may be aware of the danger and the necessity for employing a high standard of hygiene in the piggery. After the animal pens have been thoroughly cleaned by hosing it is recommended that they be treated with a hypochlorite solution* and allowed to dry. So far as it is possible, dogs should not be allowed to come into contact with the swine; the workers should be encouraged to wash and dry their hands and equipment after cleaning out the pens, and to cover immediately any cuts and abrasions with adequate protective dressings.

*Davidson and Smith (1936) found that "chloros" diluted 1 in 64 was effective in killing leptospires in premises contaminated with the urine of rats.

Summary

Five cases of canicola fever, diagnosed on clinical and serological evidence, occurred during a period of five years among piggery workers engaged in farms in the environs of Edinburgh.

A survey of 47 piggery workers in 12 Edinburgh farms showed from the results of serological examinations that 19 (40%) had at some time been infected with *L. canicola*. In addition to the five known cases this figure includes five others with histories of illness suggestive of canicola fever.

Specimens of blood from pigs from the two farms in which most of the cases occurred were found to contain antibodies to *L. canicola* in titres high enough to indicate a leptospiral infection. In one farm 46 out of 75 (61%) of the pigs were positive and in the other 40 out of 98 (40%).

Four out of six pigs newly introduced into one of the infected piggeries developed antibodies to *L. canicola* within three to eight weeks. On the 47th day after admission leptospires were being excreted in large numbers in their urine.

A hamster inoculated with the infected urine died after six days and leptospires were grown in culture from the heart blood. They were identified as *L. canicola*.

Six pigs were inoculated each by a different route with a virulent culture of *L. canicola*. Those which were inoculated subcutaneously and through a scarified area of skin developed antibodies to titres of at least 1 in 10,000 within 10 days. No obvious symptoms of disease followed the administration of the culture by any of the routes employed.

Pigs which were inoculated with urine from infected pigs subcutaneously and by scarification developed antibodies to *L. canicola* within 13 days. No symptoms other than a slight febrile reaction and a tendency to be less vigorous followed the inoculations.

The above evidence indicates that pigs may harbour *L. canicola* without showing any noticeable symptoms of disease. The organisms are excreted in the urine, and infection is passed from pig to pig. Human infection may result through contact with infected pigs.

The incidence of canicola fever in piggery workers is high, and this is in contrast to the recognized low infectivity rate among dog owners.

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NORADRENALINE IN SHOCK DUE TO VISCERAL PERFORATION

BY

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In states of shock survival of the patient ultimately depends on removing the cause of the shock. Some temporary measure to tide the patient over the hypotensive crisis is, however, often necessary to prevent the vicious circle of progressive irreversible shock, and may be absolutely essential if the patient is to survive a major surgical procedure.

The following three cases of shock associated with visceral perforation all responded only temporarily to the infusion of moderate amounts of blood and dextran, and the early use of a continuous noradrenaline infusion over a period of days appeared to play a necessary part in maintaining an adequate blood pressure and in ensuring the recovery of the patients from the condition of circulatory failure. The cases described are three consecutive cases of this type that were admitted to the Central Middlesex Hospital.

Case 1

A woman aged 66 collapsed at noon on December 22, 1955, with very severe pain in the left iliac fossa, the pain soon radiating across the whole abdomen. When seen she was grey and very ill. Her blood pressure was 95/70 and her pulse volume was poor.

An intravenous infusion was set up and 1 pint (570 ml.) of dextran was given. Her general condition improved, and immediately prior to operation (six hours after the onset of symptoms) her systolic blood pressure was 125.

Anaesthetic induction and maintenance was with nitrous oxide, trichlorethylene, and oxygen. Orotracheal intubation with a cuffed tube was performed under suxamethonium relaxation. Gallamine, 40 mg., was given, and later a suxamethonium drip was set up. Operation revealed faecal fluid and also solid faeces in the peritoneal cavity, due to a rupture of the sigmoid colon. Distal to the rupture there was an annular thickening of the wall of the bowel, this almost certainly being neoplastic in nature. The peritoneum was cleaned of faeces so far as possible and the perforated gut was delivered as a loop colostomy. After operation intensive antibiotic therapy with penicillin, streptomycin, and oxytetracycline was instituted.

After induction the systolic blood pressure rose to 130, but thence gradually fell during the course of the operation even though a further ½ pint (284 ml.) of dextran was infused. The pulse volume became very poor and eventually the systolic pressure was barely 80. The patient was cold and very pale. Intravenous injection of 14 mg. of methylamphetamine hydrochloride ("methedrine") in two divided doses produced only a slight and very transient improvement in the blood pressure. A blood infusion was then started, but no immediate improvement followed.

In order to raise the blood pressure intravenous noradrenaline was given at the conclusion of the operation. A strength of 4 mg. of the bitartrate in 1,000 ml. of dextrose–saline was used, and at 60 drops a minute the systolic blood pressure rose from 80 to 125 within a matter of minutes (Fig. 1).

Back in the ward the intravenous noradrenaline was temporarily discontinued, one hour after its commencement, to see if the blood pressure would be maintained. At this time the patient had had a total of 1½ pints (850 ml.) of

dextran and nearly 1 pint (570 ml.) of blood. There was an immediate fall in blood pressure to 90 systolic and the pulse rate rose from 140 to 160. Consequently the intravenous noradrenaline was recommenced. The blood pressure immediately rose and the pulse rate fell again.

Two hours after its commencement, the infusion was doubled in strength to 8 mg. of noradrenaline per 1,000 ml., and was utilized at this strength for the next 13 hours at a rate that varied between 32 and 80 drops a minute. Notwithstanding this, the systolic blood pressure sometimes fell to 75 and remained there at one period for four hours. The pulse volume remained very weak and the condition of the patient was poor.

Fifteen hours after operation the strength of the infusion was again doubled (now 16 mg. of noradrenaline per 1,000 ml.). At varying rates up to 60 drops a minute the systolic pressure was maintained at about 85 for the next

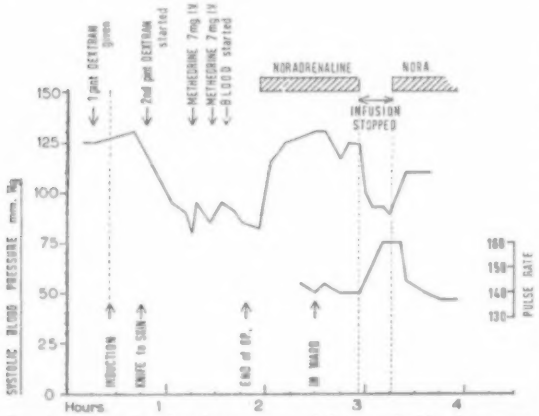

FIG. 1.—Chart showing the response of the systolic blood pressure to noradrenaline infusion (Case 1).

five hours. At 20 hours from operation the pressure rose to 100 and was maintained between 100 and 120 at 40 to 60 drops a minute. The general condition of the patient now showed some definite improvement.

Still later the strength of the infusion was increased to 32 mg. of noradrenaline per 1,000 ml. At a drip rate varying between 30 and 60, the systolic pressure was maintained fairly constantly in the region of 100. The pulse rate was 110 and the condition of the patient was now much improved.

At 40 hours from operation the drip rate was slowed to 10 and finally stopped about 47 hours after operation. Subsequently the systolic pressure was well maintained at over 110, and later became stabilized in the region of 130. The pulse rate remained about 100. The patient continued to gain strength day by day.

No further blood or dextran was given to the patient other than that received before, during, and immediately after the operation—a total of 1½ pints (850 ml.) of dextran and 1 pint (570 ml.) of blood.

The urinary output during the first post-operative 24 hours was only 8 oz. (227 ml.). During this period the systolic blood pressure was for long periods between 75 and 90. Urinary output during the second 24 hours was 33 oz. (938 ml.). During this period the systolic pressure was maintained between 100 and 130 for most of the time. Urinary output during the third 24 hours was 84 oz. (2,387 ml.).

A further operation, at a later date, revealed that the carcinoma was inoperable, and the patient went home with a permanent colostomy. Her general condition, however, was remarkably good.

Case 2

A man aged 49 on January 6, 1956, gave a history of sudden onset of acute central abdominal pain. When admitted he was in great pain and in a shocked condition. His blood pressure was 93/55 and pulse rate 140.

He was given morphine, ¼ gr. (16 mg.), and an infusion of dextran was started. Immediately prior to operation (about nine hours after the onset of symptoms) he had had 1 pint (570 ml.) of dextran and his systolic blood pressure was 100.

Anaesthetic induction and maintenance was with nitrous oxide, trichlorethylene, and oxygen. Orotracheal intubation with a cuffed tube was performed under suxamethonium relaxation. Later gallamine, 80 mg., and further suxamethonium were given. Operation revealed a large quantity of faecal fluid and lumps of solid faeces in the peritoneal cavity. There was a rupture in the wall of the sigmoid colon. The peritoneum was cleansed, the distal colon emptied of faeces, and the rupture in the sigmoid colon sutured. A transverse colostomy was performed. Following operation antibiotic therapy with penicillin and streptomycin was instituted.

Six minutes after induction the systolic blood pressure rose from 100 to 120, but thereafter there was a steady fall in pressure even though another full pint (570 ml.) of dextran was infused fairly rapidly. Towards the end of the operation the systolic pressure was 90 and infusion of blood was started. Two-thirds of a pint (380 ml.) of blood was given in 35 minutes before the patient was returned to the ward; the systolic pressure was then 100. Back in the ward the remainder of the blood was given, and the blood pressure rose to 115/70. A total of 2 pints (1,140 ml.) of dextran and 1 pint (570 ml.) of blood had then been given. The patient received no further intravenous dextran or blood.

Subsequently, however, the blood pressure progressively fell and in 75 minutes had dropped to 70/50. Intravenous noradrenaline was then begun one and a half hours after the end of the operation, and the blood pressure was raised to 100/60 in 30 minutes using a strength of 8 mg. of noradrenaline to 1,000 ml. of dextrose–saline running at 25 drops a minute. Later the drip rate had to be increased to 60 to keep the systolic pressure between 90 and 110, and at nine hours after operation the rate had to be increased to 80.

Eleven hours after operation the infusion strength was increased—to 24 mg. of noradrenaline per 1,000 ml. At 20 drops a minute the pressure fell to 70/50, but at 36 drops it was maintained fairly constantly at 100/70. The general condition of the patient was now improved.

Twenty-six hours after operation the infusion strength was again increased—to 32 mg. of noradrenaline per 1,000 ml., and a drip rate of about 40 maintained the blood pressure at approximately 115/70. Forty hours after operation the drip rate was cut down to 25 and later reduced still further. The blood pressure was maintained about 125/70 and the general condition of the patient was now fairly good.

Sixty hours after operation the noradrenaline infusion was discontinued. Although the patient had been weaned off

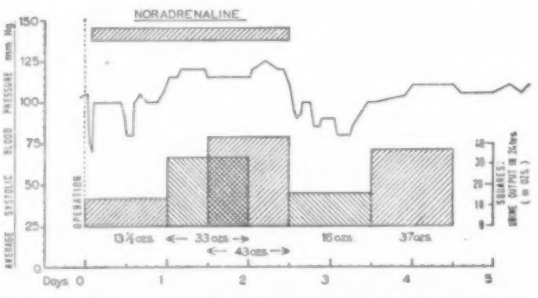

FIG. 2.—Chart showing the relationships of the blood pressure and the urinary output to the noradrenaline infusion (Case 2). Following the cessation of noradrenaline infusion there was a 24-hour period of hypertension.

this fairly gradually there was a fall in blood pressure to 90/60 and later to 80/50, the period of hypotension persisting for about 24 hours. As the condition of the patient was then good and he showed no other signs of shock it was decided not to restart the noradrenaline infusion. The blood pressure eventually rose above 100 systolic and became stabilized about 110/65.

The urinary output during the first 24 hours following operation was 13½ oz. (383 ml.) and during the second 24 hours was 33 oz. (938 ml.). Twenty-four hours before the cessation of the noradrenaline infusion the output was 43 oz. (1,221 ml.) but fell to 16 oz. (454 ml.) for the 24 hours during the period of hypotension following its cessation (Fig. 2). The input during this latter period was greater than the input of the previous 24 hours.

The colostomy was later closed and the patient eventually left hospital fit and well. A pathological state that could have accounted for the rupturing of the colon was never found.

Case 3

A man aged 75 awakened in the early hours of the morning of January 18, 1956, with severe epigastric pain which rapidly spread to the rest of the abdomen. When seen about six hours later he was in great pain and was pale and shocked. His blood pressure was 86/50 and his pulse 102.

A dextran infusion was started and morphine, ¼ gr. (11 mg.), was given. Immediately before operation (about eight hours after the onset of symptoms) he had had 1 pint (570 ml.) of dextran and his systolic blood pressure was 110.

Anaesthetic induction and maintenance was with nitrous oxide, trichlorethylene, and oxygen. Orotracheal intubation with a cuffed tube was carried out under suxamethonium relaxation; later gallamine, 60 mg., was given. Further relaxation was provided by using intermittent suxamethonium. Operation revealed a large pyloric ulcer which had perforated. Several pints of free fluid and much gas were found in the peritoneal cavity. A partial gastrectomy was performed with moderate difficulty.

Fifteen minutes after induction the systolic pressure had risen from 110 to 120. As operation began a slow blood infusion was set up. However, within the next 35 minutes the systolic pressure had fallen to 80 and consequently the rate of the blood infusion was accelerated very considerably. There was an immediate response and the systolic pressure eventually rose to 140. Following cessation of the blood infusion, however (after 1 pint (570 ml.) had been given), there was a fairly abrupt fall in pressure down to 75 systolic. Intravenous methylamphetamine hydrochloride (8 mg.) raised the systolic pressure immediately to 130, but this was very transient and a further intravenous dose of 8 mg. had to be given 20 minutes later, together with 12 mg. intramuscularly (Fig. 3). Again a good but relatively transient response was obtained.

At the conclusion of the operation voluntary respirations were relatively shallow, and while still intubated the patient suddenly collapsed, his radial pulse becoming impalpable. Whilst apparatus for a noradrenaline infusion was being assembled the patient was inflated with oxygen and recovered in under a minute, his systolic pressure returning to 110. Atropine, 1/100 gr. (0.65 mg.), and neostigmine, 2 mg., were given intravenously, and voluntary respirations definitely improved and soon appeared to be quite adequate. As the systolic pressure was being maintained over the next 15 minutes the noradrenaline infusion was withheld.

On return to the ward the patient's systolic pressure fell, and one hour after leaving the theatre was only 75—it remained about this level for two and a half hours. During this period a further ¼ pint (284 ml.) of blood was infused, but no significant rise in the blood pressure occurred. A total of 1 pint (570 ml.) of dextran and 1¼ pints (850 ml.) of blood had then been given. As the general condition of the patient was very poor a noradrenaline infusion was begun, a strength of 8 mg. of noradrenaline to 1,000 ml. of dextrose–saline being used. The infusion was run very slowly at first; the systolic pressure was gradually raised to 100 and was maintained fairly constantly at this level, running at 40 drops a minute.

Six and a half hours after the commencement of the infusion the strength of the noradrenaline was doubled (to 16 mg. of noradrenaline per 1,000 ml.) and the rate cut down to between 20 and 25 drops a minute. The systolic pressure was maintained fairly constantly at 100 to 110 and later between 110 and 120. The general condition of the patient showed marked improvement over the next 16 hours. Further steady improvement continued day by day.

The noradrenaline infusion was continued for a total of 40 hours; for most of the time the rate was approximately 20 to 30 drops a minute, the strength of solution being 16 mg. of noradrenaline per 1,000 ml. The infusion was discontinued fairly suddenly and the systolic pressure fell from a constant 120 down to 105. Within a further three hours, however, it was being maintained constantly between 115 and 120.

Twenty-seven hours after the commencement of the noradrenaline infusion the patient's pulse was noticed to be irregular. This was probably due to auricular fibrillation, but it might have been caused by multiple extrasystoles. No fall in the blood pressure occurred and the patient's general condition remained steady. Intravenous digoxin was given in the infusion. The irregular pulse persisted for over 24 hours after the time the noradrenaline was discontinued.

Owing to incontinence the exact urinary output during this period could not be accurately ascertained, but, apart from the first 24 hours, it appeared to be adequate.

On the twelfth day after operation the patient was very well and was beginning to eat a light diet. Unfortunately, in the evening he suddenly collapsed and died. Post-mortem examination revealed a pulmonary embolus.

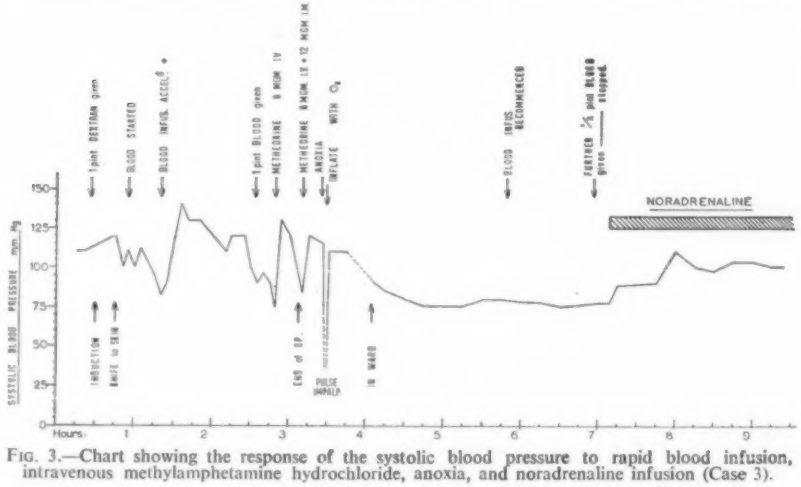

FIG. 3.—Chart showing the response of the systolic blood pressure to rapid blood infusion, intravenous methylamphetamine hydrochloride, anoxia, and noradrenaline infusion (Case 3).

Discussion

Although a systolic blood pressure below 70 or 80 mm. Hg may be tolerated for some considerable time in an otherwise fit individual, there is little doubt that in an ill and toxic patient such a hypoten-

sion persisting for more than an hour or so must seriously prejudice the chances of recovery. Therefore in ill toxic patients every endeavour must be made to raise the systolic pressure to about 90 mm. Hg or above.

In the treatment of shock due to visceral perforation simple infusions of blood or dextran alone are usually effective in permanently maintaining an adequate blood-pressure level provided that the factors causing the shock are effectively treated. Therefore, in the first instance, infusions of blood or dextran should be instituted. Should such simple measures fail, then the early use of continuous noradrenaline infusion probably holds out the best chance of recovery.

In the three cases of this series the responses to intravenous infusions of blood and dextran were initially good, but in none of them was the blood pressure maintained permanently at a reasonable level even after the infusion of moderate amounts—2½ to 3 pints (1,400 to 1,700 ml.)—of these fluids. However, intravenous noradrenaline quickly brought up the blood pressures, and, by a regulation of the rates of infusion, maintained them, by and large, at a constant satisfactory level. In the absence of some such measure to maintain a satisfactory blood-pressure level, it is possible that none of these patients would have survived. Perhaps further transfusions of blood and dextran might have achieved similar results, but they could, at the same time, have led to a dangerous overloading of the circulation. Certainly the use of very large amounts of blood would appear to be a more unphysiological line of therapy notwithstanding the limitations of noradrenaline as a pressor agent.

Objection to the use of noradrenaline in hypotensive states has been made because it is thought that, although the blood pressure is raised, the blood flow to vital organs is, owing to the completely unselective nature of the vasoconstriction produced by the pressor agent, actually reduced. This is undoubtedly true when considering the effect of noradrenaline on normotensive individuals, or on shocked subjects whose symptoms are due to reduced blood volume, but the haemodynamic response that occurs when noradrenaline is administered to a subject whose shocked sate is not associated with any significant oligaemia may not be at all times comparable, and clinical experience tends to confirm this view. The heightened level of consciousness often seen in such shocked patients as the blood pressure rises under noradrenaline therapy is strongly indicative of an increased cerebral blood flow. The vastly increased urinary output is, similarly, a strong indication that the renal blood flow has increased, although some increase in urinary output is theoretically consistent with a reduced blood flow if the filtration fraction is sufficiently increased.

No obvious change in the level of consciousness was noted in these patients, mainly, no doubt, because the infusions were started in the immediate post-operative period. A significant effect on the urinary output was, however, apparent in Case 2, and its effect on the output in the other cases was probably no less significant. In Case 2 there was a 24-hour period of hypotension following the cessation of the noradrenaline infusion (60 hours after operation), and during this period the urinary output fell dramatically notwithstanding the fact that the input was slightly greater than the input of the previous 24 hours (Fig. 2). It is therefore reasonable to infer that noradrenaline played an important part in the maintenance of an adequate urinary output, and that its effect in maintaining such an output was so great that it is reasonable to assume that renal blood flow, during the period of noradrenaline therapy, was greater than the blood flow in the period immediately after its cessation. The effect of noradrenaline on the blood flow to other vital organs was probably comparable.

The early promotion of an increase in blood flow to vital organs, including centres in the medulla, together with the correction of any myocardial ischaemia following an increase in coronary blood flow, almost certainly helps to prevent the development of an irreversible phase, refractory to treatment (including noradrenaline therapy), and progressing rapidly to complete circulatory standstill.

The need to increase progressively the dose of the drug as the duration of its administration increases may be evidence of deterioration in the condition of the patient, but it may, on the other hand, be due to the patient developing an acquired tolerance to the drug. It was met with in Cases 1 and 2, but not in Case 3. It was so marked in Case 1, where there had been such a dramatic initial response, that the systolic pressure was allowed to fall dangerously low: the strength of the noradrenaline solution should have been increased earlier than it actually was. Should this diminished response to the drug be due to acquired tolerance then it is possible that the administration of cortisone or corticotrophin might prevent it occurring.

Following induction of anaesthesia there was in all cases a slight rise in the systolic blood pressure and a marked diminution of the facial pallor. This may have been due to the removal of one of the possible factors causing the shock—namely, the severe pain. However, it is possible that more efficient oxygenation, following induction and intubation, was responsible for the temporary diminution of the signs of shock.

The paramount importance of adequate oxygenation in the shocked patient is clearly illustrated in Case 3. Here the patient collapsed after operation because voluntary respirations were too shallow for full oxygenation. Vigorous inflation with oxygen alone led to recovery in a very short time (Fig. 3). This episode underlines the need for ensuring that any respiratory depression due to relaxant drugs has been fully counteracted before extubation, and poses the question whether long-acting relaxants should be avoided in cases of shock or in very ill patients.

The noradrenaline infusions were maintained for 47, 60, and 40 hours respectively. Toxic effects attributable to the drug were not noticed.

Summary

Three cases are described in which noradrenaline had to be used in order to maintain an adequate blood pressure after traditional methods of resuscitation had failed. The cases are consecutive ones of their type. The two patients with perforation of the large bowel recovered completely; the patient with peptic ulcer perforation showed a good immediate recovery but died 12 days later owing to a pulmonary embolus.

It is suggested that in these cases of shock traditional methods of resuscitation should be tried first, but if these methods fail the use of a continuous noradrenaline infusion should not be delayed.

Noradrenaline therapy is very far from being the complete answer to the problem of the treatment of the shock due to visceral perforation, but its early use in the shocked state probably produces an increase in blood flow to vital organs. This and the correction of myocardial ischaemia (following the increase in coronary blood flow) may be important factors in helping to prevent the development of an irreversible phase which is refractory to treatment and where noradrenaline therapy is of no avail and may possibly do more harm than good.

The paramount importance of adequate oxygenation in the shocked patient is stressed.

My thanks are due to Mr. T. G. I. James for permission to publish Cases 1 and 3 and to Mr. J. D. Fergusson for permission to publish Case 2—under whose care these patients were respectively; to Dr. R. D. Levis for his interest and help; to others who have offered help and criticism; and to Mrs. I. M. Prentice, of the department of medical art, who produced the charts.

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REPORT OF TWO SIBLINGS DIAGNOSED AS CASES OF ACUTE LYMPHATIC LEUKAEMIA

BY

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The cases described below concern a brother and sister in both of whom acute lymphatic leukaemia was diagnosed during life. In the sister the disease followed a classical course to an early death, but in the brother, although he too died after a short illness, certain unusual features were noted during life and at necropsy. This report is presented because of the rarity of familial leukaemia and because of the interest of the case of the brother.

Case 1

The patient, a housewife aged 38, was admitted to West Middlesex Hospital early in March, 1950, because of pallor, generalized pains and weakness developing during the last three months, epistaxes, and the passage of blood clots per vaginam apart from normal menstruation. There was nothing relevant in the past history. Results of blood examination on March 3 were: haemoglobin 53% (Haldane); R.B.C. 2,390,000 per c.mm. Total white cell count not available, but differential count showed polymorphs 12%, lymphocytes 71%, prolymphocytes 9%, and nucleated R.B.C. 8%.

Clinical examination revealed a pale woman with bilateral subconjunctival haemorrhages and suborbital bruising, petechiae, and bleeding gums. There was no lymphadenopathy, but spleen and liver were each enlarged to two fingerbreadths and were tender; two small haemorrhages were noted in the left optic fundus. Blood pressure was normal, the urine clear, and the temperature 99.6° F. (37.55° C.). Blood examination on March 10 showed: haemoglobin 34%; R.B.C. 1,200,000 per c.mm.; W.B.C. 50,700 per c.mm. (polymorphs 2.5%, lymphocytes 77%, lymphoblasts 20%).

The patient's condition rapidly deteriorated, with epistaxes, haematemeses, and melaena, and she died in cardiac failure on March 17, 1950.

Case 2

This patient, a brother of Case 1, aged 31, was admitted to King Edward Memorial Hospital, Ealing, on July 5, 1955. He had first complained of lumbar pain, with swollen inguinal and axillary lymph nodes, eight weeks previously, and at that time was thought to be suffering from glandular fever. There was no history of past illness. On June 8 a blood count revealed: haemoglobin 94%; W.B.C. 6,000 per c.mm. (polymorphs 10%, lymphocytes 89%, monocytes 1%), some large and atypical lymphocytes being similar to those seen in glandular fever.

Two weeks later severe gingivitis and some petechiae on the left arm developed. Cervical and submandibular lymph nodes swelled and he became pyrexial. On June 24 the blood count was: haemoglobin 78%; W.B.C. 7,000 per c.mm. (polymorphs 56%, lymphocytes 36%, monocytes 4%, eosinophils 3%). No atypical "glandular fever" cells noted.

On his admission to hospital on July 5 the patient was pale and had visibly enlarged cervical and submandibular lymph nodes. There were no abnormalities in the cardiovascular or respiratory system. The tip of the spleen was just palpable, but the liver was not enlarged. There was generalized lymphadenopathy, also generalized petechiae becoming confluent over chest and abdomen. Temperature was 101° F. (38.3° C.). Blood picture on admission: haemoglobin 57%; R.B.C. 4,400,000 per c.mm.; W.B.C. 3,400 per c.mm. (atypical non-granular immature cells 27%, neutrophils 6%, lymphocytes 67%); platelets 166,000 per c.mm. On sternal marrow puncture large numbers of primitive leucocytes (blast cells) and a very few normal elements were found (Fig. 1). Blood was transfused repeatedly, but no remission occurred. In view of the low total leucocyte count the patient was not given radiotherapy, or any drugs, apart from sedatives. He steadily became weaker, and on July 26 a severe throat infection with monilia occurred which did not respond to treatment.

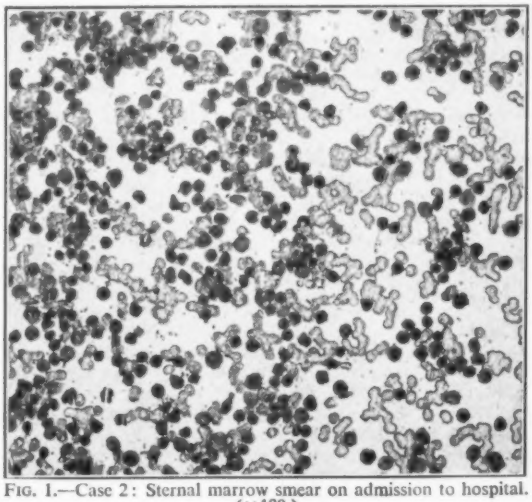

FIG. 1.—Case 2: Sternal marrow smear on admission to hospital. (×180.)

By August 1 the lymph nodes had rapidly decreased in size and then remained so. Clinically the spleen did not appear to enlarge further. A swinging temperature—98°–101° F. (36.7°–38.3° C.)—was maintained throughout the illness. A blood count on July 27 showed: haemoglobin 70%; W.B.C. 2,400 per c.mm. (lymphoblasts 20%, polymorphs 14%, lymphocytes 64%, monocytes 2%); and on July 30: haemoglobin 57%; W.B.C. 1,400 per c.mm. (differential count as before). The blood picture continued to deteriorate, and on August 10 the figures were: haemoglobin 25%; W.B.C. 800 per c.mm. (lymphoblasts 8%, polymorphs 6%, lymphocytes 84%, monocytes 2%). The patient died two days later.

Comment

There is no other family history of leukaemia, but the father and a brother and sister, who are alive and well, state that the patients' maternal grandfather died of a "rare disease." Their mother was said to have died "at the menopause," and she lost three infants before the birth of the two patients and the surviving brother and sister, the cause of their death being unknown.

Unfortunately no post-mortem examination was held on the woman. The following is taken from the necropsy report (Dr. W. S. Killpack) on her brother: "Emaciated

young adult male, slightly jaundiced. *Cardiovascular System:* Heart as a whole, dilated; pericardium healthy, no haemorrhages; myocardium very pale but fairly firm; endocardium healthy; vessels healthy. *Respiratory System:* Lungs very bulky due to oedema; numerous emphysematous bullae in right upper lobe; extensive congestion of lower lobes, ? also interstitial haemorrhage; no pneumonia found. Air passages: Some frothy mucus present; thrush membrane on epiglottis and vocal cords. Pleurae dry; fibrin over left lower lobe. *Alimentary System:* Tongue clear; extensive thrush membrane on pharynx. Oesophagus dilated with almost cylindrical, firm thrush membrane. Stomach dilated, healthy. Small gut: a few ulcers up to 1 cm. diameter in terminal ileum. Large gut: similar ulcers with membrane in caecum and descending colon. Liver (2,200 g.): normal pattern; cut surface rather brown. Gall-bladder distended with watery bile. Pancreas healthy. *Urogenital System:* Kidneys (320 g.) generally pale, marked cloudy swelling, number of pin-point haemorrhages. Bladder healthy. Genital organs healthy. Spleen (170 g.): cut surface congested, normal pattern. Lymph nodes: all groups enlarged to about twice normal size except those on lesser curvature of stomach, which were firm and greatly enlarged. Bone marrow uniformly pink and creamy. Adrenals oedematous; complete lipoid depletion. Thyroid healthy."

The histological report is as follows. Sternal marrow practically acellular; oedematous young connective tissue with small collections of lymphocytes and plasma cells and histiocytes; occasional groups of undifferentiated cells (Fig. 2). Spleen: Extramedullary haematopoiesis and siderosis without fibrosis; widespread infiltration by histiocytes (? reticulum cells), many multinucleate; undifferentiated cells here also scattered in small groups. Kidney: small focus of proliferating histiocytes or reticulum cells,

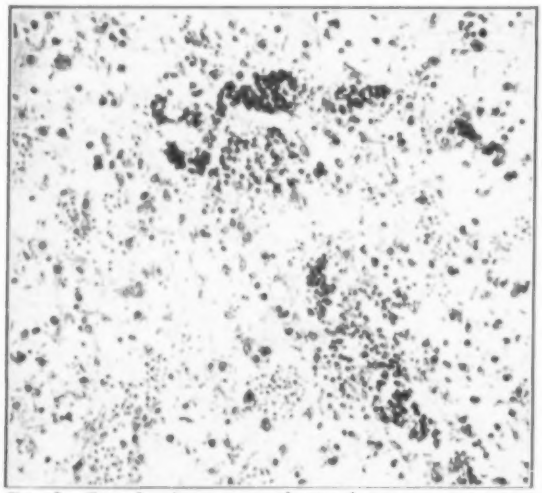

FIG. 2.—Case 2: Appearance of sternal marrow smear post mortem. (×180.)

with some new connective-tissue formation. Lung: oedema and "monocytic pneumonia." Oesophagus: monilial oesophagitis. Liver: some fatty change; no obvious infiltration.

Discussion

The interesting features of the brother's case were the rapid regression of the enlarged lymph nodes, and the change in the sternal marrow from being full of proliferating primitive cells to being virtually empty of everything but connective tissue. The enlarged submandibular and cervical nodes were very prominent at the time of his admission and subsequently. Their size diminished rapidly, literally overnight, so that by the morning of August 1, 1955, his face had resumed its normal contours. What had happened during the course of a few hours to the cellular or other tissues responsible for these swellings? And what had happened to the cells crowding the marrow cavity? Two possible diagnoses might be considered: (1) atypical reticulum-cell sarcoma with bone-marrow depression; and (2) acute lymphatic leukaemia with atypical termination. But both seem rather unlikely, for in effect there was little sign of either condition at necropsy, especially in the histological sections. No record of a similar case has been found, and it is considered that no recognized diagnosis can be applied to the present case. The case perhaps illustrates the point made by Marshall (1956), that "owing to the effects of specialisation in peripheral blood and bone marrow studies there is still a tendency to regard leukaemia as a separate disease entity instead of as a symptom in a number of neoplastic reticular tissue proliferations."

The rarity of familial leukaemia is shown by a comparison between the number of cases reported in the literature and the total number of deaths from leukaemia, which in England and Wales alone averages over 2,000 a year, the figures for 1952, 1953, and 1954, as given by the Registrar-General in his quarterly returns, being respectively 2,043, 2,121, and 2,160. By contrast there have been only about 110 cases of familial leukaemia reported in the world literature since the first descriptions of leukaemia in 1845 (Virchow; Bennett; Craigie). The first authenticated case of familial leukaemia which Videbæk (1947) allows was described by McGavran in 1922 and included in Petri's 1933 review.

Videbæk's appears to be the last review of the literature on familial leukaemia to have been published; this author found 82 leukaemic subjects in all age groups belonging to 37 different families, in none of which was there consanguinity. Since its publication, so far as I can ascertain, another 28 unquestionable cases in 12 families (excluding cases without supporting laboratory evidence) have been reported (Frech, 1948; Riel, 1948; Barbier *et al.*, 1949; Smith and Horne, 1950; Anderson, 1951; Bieber, 1951; Debré *et al.*, 1951; Portmann and Robinson, 1951; Reilly *et al.*, 1952; Stobbe and Taeschner, 1952; Ward *et al.*, 1952).

Summary

The cases of a brother and sister diagnosed in life as suffering from acute lymphatic leukaemia are reported, with a discussion of certain unusual aspects of one of the cases. Both patients died.

Brief reference is made to cases of familial leukaemia reported in the world literature.

I wish to thank Dr. J. W. Litchfield, under whose care Case 2 was admitted, for permission to publish. Case 1 was under the care of the late Dr. J. A. Torrens. I would also thank Dr. W. S. Killpack (who performed the necropsy in Case 2) and Dr. R. R. Wilson for their opinions on the bone-marrow smears and necropsy sections, and am greatly indebted to Dr. R. R. Wilson for help in preparing the article.

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TWO CASES OF RUPTURE OF THE EXTRAHEPATIC BILE DUCTS

BY

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Closed abdominal injuries that are not rapidly fatal rarely cause damage to the extrahepatic bile ducts. The cases of two children are described in whom, as a result of a traffic accident, there was leakage of bile into the peritoneal cavity, which ceased spontaneously without any local repair at operation.

Case 1

A deaf boy of 5 years was run into by a car in March, 1952. He was struck on the left side and thrown to the side of the road. On admission to the Royal Belfast Hospital for Sick Children he was pale, with a pulse rate of 160 and a blood pressure of 60/30 mm. Hg. There was no superficial bruising. His abdomen was tender and diffusely rigid. *X*-ray examination of his chest and abdomen revealed nothing abnormal. After a blood transfusion his general condition greatly improved.

At laparotomy five hours after the injury about 15 oz. (430 ml.) of blood was evacuated from the abdominal cavity. The only other abnormality discovered was a large haematoma distending the right half of the lesser omentum in its free margin; neither the spleen nor the liver had been torn. As bleeding had already ceased nothing further was done and the abdomen was closed without drainage.

His condition was satisfactory until the eighth post-operative day, when a faint tinge of jaundice appeared; it progressed steadily and was accompanied by increased bile pigment in the urine and absence of stercobilin from the faeces. At the same time the abdomen became so distended with fluid that between the fourth and eighth post-operative weeks it was aspirated four times, in all about 7 pints (4 litres) of heavily bile-stained but uninfected fluid being removed. By the end of the eighth post-operative week the abdominal swelling had subsided, the jaundice had gone, the excessive bile pigment had disappeared from the urine, and normal pigmentation had returned to the faeces. Throughout these eight weeks he made no complaint of abdominal discomfort, had a moderate appetite, and never had any abdominal tenderness or rigidity other than in the operation wound. When last seen (January, 1956) he was in excellent health.

Various investigations were undertaken. The liver-function tests showed no abnormality: bromsulphthalein test, 1% retention after 45 minutes; total serum proteins, 7.2 g. per 100 ml. (albumin 5.3 g., globulin 1.9 g.); serum alkaline phosphatase, 6.9 King–Armstrong units; serum bilirubin, 0.2 mg. per 100 ml. The blood picture was normal: Hb, 11.9 g. per 100 ml.; white cells, 9,520 per c.mm.; platelets, 253,000 per c.mm. "Biligrafin" visualization of the biliary tract showed no abnormality.

Comment.—The injury damaged some part of the extrahepatic biliary system which, for a while, allowed all or almost all the bile it transmitted to leak into the peritoneal cavity, from which it was aspirated or absorbed. The absence of stercobilin from the faeces suggests that for probably about six weeks the bile was all either diverted or obstructed. With no operative treatment the biliary passages re-established their continuity.

Case 2

A boy aged 6 years was admitted to hospital on December 10, 1953, after being hit by a car. On admission he was severely shocked, showing signs of internal haemorrhage from a closed abdominal injury. A radiograph of the chest and abdomen showed no abnormality. After blood transfusion his general condition greatly improved.

At laparotomy through an upper midline incision six hours after the injury a considerable amount of blood was found in the abdominal cavity. As the spleen was found to be torn, splenectomy was performed. A tear of the liver 2 in. (5 cm.) long and ¼ in. (6 mm.) deep was found in the groove for the falciform ligament. A large haematoma, as in the previous case, distended the right half of the lesser omentum and there was a tear in the centre portion of the lesser omentum (see Fig.). A retroperitoneal haematoma was present, extending over the pancreas and the left kidney. Haemostasis was secured and the abdomen was closed with drainage.

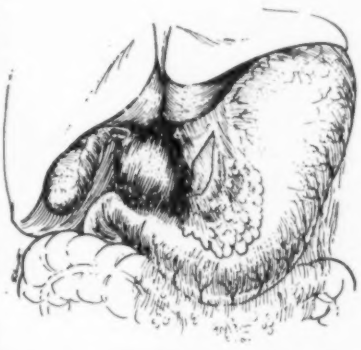

Diagram showing haematoma in the right half of the lesser omentum and a tear in its central portion (Case 2).

The general condition remained good, but within two days a biliary fistula formed at the drainage site. After draining profusely for about three weeks it dried up spontaneously. The faeces remained normal, no excess bile pigment appeared in the urine, and there was no sign of jaundice. The abdomen did not distend.

The patient has remained a healthy schoolboy with no abnormality detectable on physical examination. Biligrafin *x*-ray films show no abnormality of the biliary tract.

Discussion

Injury to the extrahepatic ducts is a rare surgical problem, probably because the associated injury to neighbouring structures causes early death. Fewer than 100 cases were recorded in the last century (Mason, Sidbury, and Guiang, 1954). The present two cases are the only ones in the records of the Royal Belfast Hospital for Sick Children for the last 25 years.

The extrahepatic ducts can be injured by direct violence from crushing against the vertebral column, but our first case and that described by Benson and Prust (1953) both received blows on the left side. Possibly the injury was caused by indirect violence as a result of sudden stretching of the structures in the right (free) border of the lesser omentum following flexion of the trunk to the left.

Both cases presented with signs of intraperitoneal haemorrhage, which before operation was thought to be due to rupture of the spleen or liver. In each a large haematoma completely obscured the anatomy in the region of the free border of the lesser omentum, and in neither was it thought advisable to disturb it. It may be that in each case the presence of the haematoma prevented the escape of bile at the time of laparotomy and that only as the haematoma was absorbed was bile able to leak out. Another possibility is that the wall of the duct sloughed later.

The escape of sterile hepatic-duct bile into the peritoneal cavity does little harm (Harkins, Harmon, and Hudson, 1936), causing an exudation of some fluid and a slight rise in pulse and temperature. Both of our cases had post-operative escape of bile into the peritoneal cavity without any general systemic upset. The drain in Case 2 allowed the bile to escape, preventing abdominal distension. In this case also a small tear was present in the liver which could have allowed the escape of bile; but since the discharge was so copious and prolonged, and since the haematoma in the

lesser omentum was exactly similar to that in our previous case, we feel that an extrahepatic duct must have been torn.

A partial or complete tear may occur in the extrahepatic ducts which may or may not be obvious at the time of operation. Many forms of surgical treatment have been advocated. Waugh (1916) had a case, very similar to our first, in which two laparotomies were carried out for upper abdominal distension and signs of obstructive jaundice and in which the condition suddenly cleared up spontaneously. Benson and Prust (1953) treated a case successfully by marsupialization and drainage of a false cyst of biliary ascitic fluid which had formed. Gross (1953) had two cases; one was treated successfully by simple drainage from the site of the injury, while in the other an attempt was made at primary repair. Stenosis of the common bile duct, however, developed, necessitating cholecysto-duodenostomy, which led to cholangitis, cirrhosis, bleeding oesophageal varices, and death. Mason *et al.* (1954) had a case which developed stenosis requiring cholecysto-duodenostomy even though no attempt at repair had been made at the primary operation. Hicken and Stevenson (1948) advocated a cholecystostomy to decompress the biliary system, and suggested that cholangiograms could be taken later to demonstrate healing of the tear and also to make sure that any associated traumatic pancreatitis which might obstruct the lower end of the common bile duct had settled before removing the tube.

It is quite clear that injuries to the extrahepatic ducts often heal spontaneously without the development of stenosis, and it is possible that an attempt to repair a recently traumatized duct may increase the likelihood of stenosis. Simple abdominal drainage, and possibly cholecystostomy, should be performed initially; if stenosis develops it can be treated later.

Summary

Two cases of rupture of the extrahepatic bile ducts are described in which the lesion was not recognized at operation. Biliary ascites with minimal systemic upset developed in one, necessitating frequent aspiration. In the other a drainage tube allowed the bile to escape externally. Spontaneous healing of the fistula occurred in both.

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The General Register Office's analysis of the occupations of persons in England and Wales included in the 1951 Census has been published as *Census 1951, England and Wales, Occupational Tables* (H.M.S.O., price seven guineas). It is based on the full figures, thus replacing the results of the 1% sample published in 1952. The findings are compared with those of the 1931 Census. Owing to the difference in school-leaving age at the times of the Censuses, the 1931 occupational figures include some 285,000 children under 15, while the 1951 figures relate to those over that age. In 1951 14 million of the 16 million males were gainfully occupied, and 6¼ million of the 18 million females. Of the occupied men, 29% were under 30 and only 4% over 65; of the occupied women, 44% were under 30 and 5% over 60. In 1951 there were 11 million married women, of whom 22% were gainfully occupied compared with 10% in 1931. The two commonest occupations for the married women were as charwomen and clerks—149,000 of each.

THE ANTIBACTERIAL ACTIVITY OF CHLOROPHYLL

BY

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Numerous reports have been published describing the successful treatment of chronic infected wounds with water-soluble chlorophyll preparations. In many cases healing has been induced where there had been no response to conventional treatment. Bowers (1947) treated 400 various surgical cases with water-soluble chlorophyll and noticed that infected wounds became free from suppuration and odour within two or three days. Combes, Zuckerman, and Kern (1952) produced a similar reduction in suppuration in secondarily infected ulcers, contact dermatitis, and pemphigus. Carpenter (1949) observed an early eradication of infection and early healing in 127 cases of suppurative osteomyelitis and chronic ulcers: the healthy appearance of granulation tissue under chlorophyll therapy was stressed.

Whereas chlorophyll derivatives in wound healing are generally regarded as promoters of healthy granulation, some clinical reports suggested that they have antibacterial properties. Smith (1944) observed *in vitro* bacteriostasis of staphylococci, streptococci, and the anaerobic spore-bearers, while Nevin and Bibby (1954) showed that chlorophyll inhibited the growth of staphylococci, streptococci, and lactobacilli.

The present experiments were designed to investigate further, by *in vitro* methods, the antibacterial activity of a chlorophyll preparation.

Material and Methods

The water-soluble chlorophyll preparation used throughout these experiments was sodium potassium copper chlorophyllin (which is the base of "chloresium" preparations) kindly supplied by Rystan Company, New York. A fresh 10% solution was prepared daily in sterile distilled water, and dilutions of this used in all experiments.

The sensitivity of various organisms to chlorophyll was determined, using a plate method modified from that described by May and Morley (1952). Levinthal agar was used throughout. All organisms were grown in nutrient broth for five hours and the standard inoculum was one loopful, approximately 10^5 organisms. Plates were incubated aerobically for 16 hours at 37° C. The highest concentration of chlorophyll incorporated in solid media was 1/100. This was governed by the solubility of the preparation; a 10% solution was the maximum concentration possible.

Chlorophyll sensitivity was also determined by making bacterial counts of organisms growing in fluid media. Growth curves were plotted by the method of Miles, Misra, and Irwin (1938), with organisms grown in nutrient broth containing dilutions of chlorophyll.

Results

Sensitivity of Various Organisms to Sodium Potassium Copper Chlorophyllin.—The results of the plate method are shown in Table I. Chlorophyll was found to inhibit the growth of some Gram-positive bacteria, but had no effect on the Gram-negative organisms tested. No change in antibacterial properties was produced by heating the chlorophyll at 100° C. for one hour. The presence of 10% horse serum in the medium did not affect the inhibitory level. Since *Staph. aureus* is a common wound contaminant it was chosen as the test organism for all further experiments.

TABLE I.—*Sensitivity of Various Bacteria to Chlorophyll*

Organism	Inhibitory Level of Chlorophyll	Organism	Inhibitory Level of Chlorophyll
Staph. aureus	1/800	*Cl. welchii*	1/200
Staph. albus	1/800	*Cl. oedematiens*	1/100
Str. pyogenes	1/1,600	*Cl. sporogenes*	1/100
Str. viridans	not at 1/100	*Cl. tetani*	1/100
Str. faecalis	not at 1/100	*Ps. pyocyanea* ..	not at 1/100
Pneumococcus	1/1,600	*Pr. vulgaris*	not at 1/100
B. pumilis	1/800	*E. coli*	not at 1/100

Sensitivity of Different Strains of Staph. aureus.—Thirteen strains of *Staph. aureus* were streaked over chlorophyll-Levinthal agar: five were inhibited at a chlorophyll concentration of 1/800, seven at 1/400, and one at 1/100.

Effects of Age of Culture, Time of Inoculation, and Size of Inoculum.—Cultures of one strain of *Staph. aureus* incubated for 2, 4, 6, 8, and 24 hours were plated out on chlorophyll-Levinthal agar. A dilution of 1/800 chlorophyll inhibited growth after 16 hours' incubation in every case. After 24 hours' further incubation *Staph. aureus* grew in the presence of all concentrations of chlorophyll. It appears, therefore, that either chlorophyll is inactivated at 37° C. or it does not completely inhibit growth. Chlorophyll-Levinthal agar maintained at 37° C. for 24 hours before use still inhibited growth for 16 hours at a concentration of 1/800. Hence growth of the test organism after long incubation periods is not due to inactivation of the chlorophyll. The organisms are temporarily inhibited, but after 24 hours bacterial multiplication proceeds. The size of inoculum, ranging from 10^6 to 10^2 organisms, did not affect the inhibitory level.

Growth of Staph. aureus in the Presence of Chlorophyll.—The growth curves shown in Fig. 1 confirmed the conclusion drawn from the results of the plate method that chlorophyll

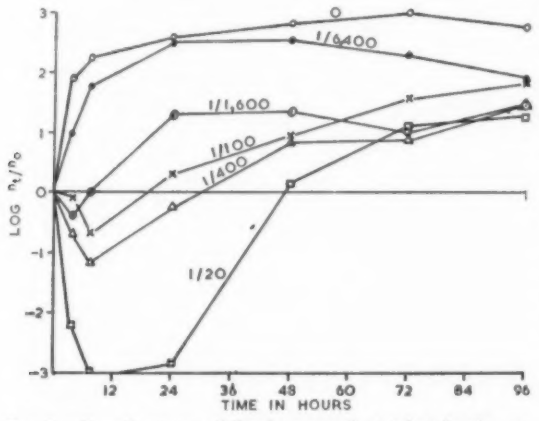

FIG. 1.—Growth curves of *Staph. aureus* in nutrient broth containing various concentrations of chlorophyll. n_t = Number of organisms per ml. at time t. n_o = Number of organisms per ml. at start of experiment.

temporarily inhibits the growth of *Staph. aureus.* Some organisms were killed, the number increasing with chlorophyll concentration, but even when this was 1/20 bacterial multiplication began after 24 hours. Thus it seems that *Staph. aureus* became resistant to chlorophyll. The emergence of chlorophyll resistance could not be demonstrated by the usual methods because the solubility of the preparation is such that a concentration completely inhibiting the organism for indefinite periods could not be used. However, *Staph. aureus* was grown on Levinthal agar containing 1/100 chlorophyll by incubating at 37° C. for 48 hours. After eight subcultures of successively reduced incubation periods the organism grew well in the presence of 1/100 chlorophyll after 16 hours at 37° C. It therefore seems that some form of resistance to chlorophyll is acquired.

Copper Content of Sodium Potassium Copper Chlorophyllin.—The copper content of the chlorophyll preparation used was 4.16%, and it was thought that its bacteriostatic properties might be due to the copper present. Three different organisms were cultured on two batches of Levinthal agar, one containing dilutions of chlorophyll and one containing copper sulphate in concentrations such that the two batches of medium contained identical amounts of copper. The results are shown in Table II. It may be concluded that the antibacterial properties of chlorophyll are not due to its copper content.

TABLE II.—*Comparison of Sensitivity of Three Organisms to Chlorophyll and Copper Sulphate*

Organism	Inhibitory Level of Chlorophyll	Inhibitory Level of $CuSO_4$*
Staph. aureus	1/800	>1/100
Staph. albus	1/800	>1/100
Str. pyogenes	1/1,600	1/200

* Expressed as concentration of chlorophyll containing same amount of copper.

Effect of Chlorophyll on Bacteriostasis Produced by Antibiotics

The bacteriostatic effect of chlorophyll is slight, and it was thought that it might be better demonstrated by the use of synergism, as in the method described by Dye, Lynch, Cullen, and Sprague (1952). They increased the sensitivity of the agar diffusion assay of viomycin by incorporating sulphadiazine in the medium. The possible potentiating effect of antibiotics on the antibacterial activity of chlorophyll was investigated, using a routine plate assay method. Two-layer plates were poured. Both layers contained a subinhibitory level of penicillin, and the surface layer was seeded with an inoculum of an overnight *Staph. aureus* culture sufficient to produce confluent growth. Six porcelain cylinders were placed on the surface of each plate and were filled wth equal volumes of different dilutions of chlorophyll. The plates were incubated for 16 hours and the diameters of the zones of inhibition around each cylinder were measured. The square of the diameter of the zone of inhibition was plotted against the log. of the concentration of chlorophyll.

Subinhibitory concentrations of penicillin incorporated in the medium were found to increase only slightly the zones of inhibition of growth of *Staph. aureus* produced around porcelain cylinders containing chlorophyll. The small size of zone of inhibition around a chlorophyll solution is probably due in part to the low diffusibility of the preparation; the green colour does not extend far beyond the porcelain cups. Hence the two substances were reversed; a subinhibitory concentration of chlorophyll was incorporated in the medium, and penicillin dilutions were put in the porcelain cylinders. A marked difference was observed in zone diameter between those produced on assay media containing chlorophyll and those on straight assay media. The same effect was demonstrated with oxytetracycline (" terramycin ") and streptomycin, using *B. pumilis* as the test organism for oxytetracycline and *Staph. aureus* for streptomycin.

These findings are demonstrated graphically in Figs. 2, 3, and 4. It is obvious that subinhibitory concentrations of chlorophyll in the medium cause a vertical shift in the dose-response curves for penicillin, streptomycin, and oxytetracycline.

Growth curves were plotted of *Staph. aureus* growing in nutrient broth in the presence of penicillin alone, chlorophyll alone, and combinations of the two. No synergistic effect could be demonstrated as in the agar diffusion method. Therefore it appears that the increase in sensitivity of the agar diffusion assay of antibiotics produced by subinhibitory concentrations of chlorophyll is due to some physical property of the preparation and is not true synergism. Chlorophyllin is a surface-active agent, and may, by virtue of this property, increase the sensitivity of organisms to antibiotics under the conditions of an agar diffusion assay. Smith and Livingston (1945) found that experimental wounds

treated with chlorophyll and antibiotics healed more quickly than when treated with either agent alone. This effect may partly be due to an enhancement of the antibiotic's activity by the surface active properties of the chlorophyll.

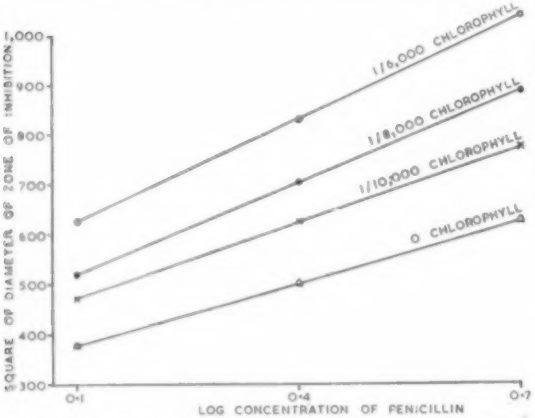

FIG. 2.—Inhibition of *Staph. aureus* by penicillin in the presence of three concentrations of chlorophyll.

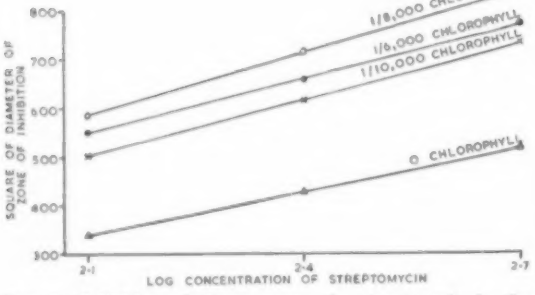

FIG. 3.—Inhibition of *Staph. aureus* by streptomycin in the presence of three concentrations of chlorophyll.

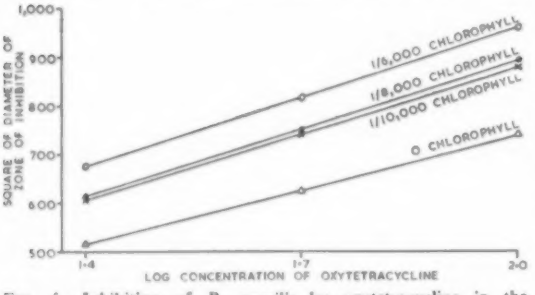

FIG. 4.—Inhibition of *B. pumilis* by oxytetracycline in the presence of three concentrations of chlorophyll.

Summary

Soluble sodium potassium copper chlorophyllin (which is the base of "chloresium" preparations) shows some bacteriostatic action against certain Gram-positive organisms, including *Staph. aureus, Str. pyogenes,* the pneumococcus, and the pathogenic clostridia. After a period of bacteriostasis, bacterial multiplication proceeds in the presence of all concentrations of chlorophyll tested.

After repeated culture in the presence of chlorophyll *Staph. aureus* becomes resistant to the temporary bacteriostatic effect of this substance.

The activity of some antibiotics is potentiated by the presence of subinhibitory concentrations of chlorophyll.

This work was carried out during the tenure of a research grant from Rystan Company, New York.

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Medical Memoranda

Rupture of the Uterus Involving the Bladder

Ruptured uterus involving the bladder is a very rare condition. It is more likely to be met with after a previous caesarean section in which the bladder is firmly adherent to the uterine scar. The following case is of unusual interest in that the patient had had no previous operation and gave no history to indicate that the bladder might be adherent to the lower uterine segment. Nevertheless she sustained an extensive tear of the uterus and the bladder during labour, which resulted in the baby's shoulder being lodged in the bladder cavity.

CASE REPORT

The patient, a Yoruba of Western Nigeria aged about 36, was admitted into Massey Street Maternity Hospital, Lagos, Nigeria, on November 16, 1954, with a history of nine months' amenorrhoea and labour pains which had started 18 hours previously. She was a gravida 4, para 3, one alive; the last confinement being three years before admission. Previous pregnancies and deliveries had been uneventful. Her general condition on admission was fair, although she appeared dehydrated. Her temperature was 99° F. (37.2° C.), pulse 120, respirations 24, and B.P. 130/70.

The bladder appeared to be full and was palpable up to the level of the umbilicus. The fundus uteri was level with the ensiform cartilage. The abdomen was very tense and the foetal parts were difficult to palpate. The foetal heart was not heard. Vaginal examination revealed slight bleeding, an almost fully dilated os, with a thick rim of cervix felt posteriorly, and the presentation was a face jammed in mid-cavity. The suspicion of ruptured uterus was confirmed when blood escaped during an attempt to pass a catheter by displacing the head upwards.

At operation blood-stained fluid was found in the abdominal cavity. The bladder peritoneal reflection was raised, dark purplish, and oedematous. When this was opened blood clots were exposed and a longitudinal tear in the lower uterine segment was seen. On reflecting the bladder from the uterus the baby's shoulder came into view and the glistening mucous lining of the bladder was observed. It then became apparent that the bladder was involved in the rupture.

Examination of the damage revealed a longitudinal tear in the lower uterine segment and a T-shaped tear in the bladder, the longitudinal arm of which extended downwards, splitting the trigone of the bladder symmetrically in two and involving the upper third of the urethra.

A subtotal hysterectomy was performed and the bladder repaired with a No. 0 chromic catgut suture. The patient's condition was satisfactory throughout and she appeared very little shocked in spite of the extensive damage. An indwelling catheter was inserted and the abdomen drained. The patient made an uninterrupted recovery but developed

a urethro-vaginal fistula, which was successfully repaired two months after the operation for ruptured uterus.

I am indebted to the Chief Medical Adviser to the Federal Government of Nigeria for permission to publish this case.

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Perforated Duodenal Ulcer Complicating Prednisolone Therapy

Many instances of serious gastro-intestinal complications occurring during treatment with prednisone and prednisolone have been recorded. Bollet *et al.* (1955) and Boland (1956) found a high incidence of peptic ulceration in rheumatoid arthritis patients treated with these drugs. Kofman *et al.* (1956) reported peptic ulceration as a complication of prednisolone treatment for metastatic breast cancer. Muller (1955) and Bickel (1955) described two cases of intestinal haemorrhage on prednisone. Gluck *et al.* (1955) treated a case of rheumatic carditis with a combination of cortisone, prednisone, and prednisolone; at necropsy a large gastric ulcer was found which had been symptomless. They also briefly described a case of perforated duodenal ulcer after seven days on prednisone. Fentress *et al.* (1956) reported the case of a rheumatoid patient on prednisone who had a perforated duodenal ulcer, and Pickert (1956) a fatal case during treatment for scleroderma.

Of 11 patients with rheumatoid arthritis treated by us with these steroids, four had severe gastric irritation necessitating treatment and reduction in dose, and one treated with prednisolone had a perforated duodenal ulcer. The latter is the subject of this report.

CASE REPORT

A 50-year-old married woman, first seen in January, 1950, had rheumatoid arthritis, established by clinical, laboratory, and *x*-ray findings. During the next three years she was twice admitted to hospital, but in spite of the usual treatments, including rest, analgesics, blood transfusions, gold, and phenylbutazone, her condition did not improve. During her second stay in hospital (June, 1951) intramuscular corticotrophin was given for 21 days with definite benefit. As the drug was scarce at that time it had to be discontinued.

Cortisone therapy, 75 mg. daily, was begun in January, 1953, and she improved greatly over the next six months. Then increasingly larger doses—up to 125 mg. daily—were needed and the drug was finally discontinued in December, 1953, because of her lack of response and a troublesome gain in weight. Her condition waxed and waned until August, 1955, when she had so deteriorated that cortisone—a replica of the first course—was recommenced. In November, 1955, she was admitted to hospital for the fourth time. Examination then showed a moon-faced, severely crippled woman, with advanced rheumatoid changes in the hands, wrists, elbows, shoulders, knees, ankles, and feet. Cardiovascular, respiratory, central nervous, and gastro-intestinal systems were normal. A blood examination showed: Hb, 70%; W.B.C., 10,000 (normal differential count); E.S.R., 83 mm. in one hour (Westergren); serum sodium, 144.7 mEq/l.; serum potassium, 4.98 mEq/l. *X*-ray examination: chest normal; joints showed advanced rheumatoid changes.

Prednisolone, 20 mg. daily, was begun on November 21. For the first three weeks the pain was lessened and there was a slight increase in mobility. She then received this treatment as an out-patient. On January 17, 1956, she had epigastric pain lasting only a few days. On January 31 joint pain and stiffness had increased, and, as there had been no recurrence of epigastric pain, the dose was stepped up to 25 mg. daily.

On February 3 she was admitted to hospital because of the sudden onset of severe pain in the right hip 12 hours previously. There was no history of trauma. The right leg was held in a position of external rotation, with limitation of all movements. *X*-ray examination showed a fracture through the neck of the right femur, with some absorption of the neck and considerable upward displacement of the shaft. It was decided to apply skin traction as a first measure, and full sedation was given. That evening she became pyrexial (102° F.; 38.9° C.), with a pulse rate of 122 and respirations 28, and during the night she vomited 30 oz. (850 ml.) of bile-stained fluid. Nausea and vomiting continued throughout the next day.

An intravenous infusion of N/5 saline was begun, a Ryle tube passed, and systemic penicillin given. Her condition improved, and still no localizing signs could be elicited in the abdomen. Straight *x*-ray examination of the abdomen showed no abnormality. Investigations on this day gave Hb, 74%; W.B.C. 14,500 (82% polymorphs, 16% lymphocytes); serum sodium 135 mEq/l.; potassium 4.7 mEq/l.; chlorides, 93 mEq/l.; blood urea, 39 mg./100 ml.

On the morning of February 7 the patient's condition was regarded as satisfactory. Her temperature, pulse rate, and respirations were normal, and electrolyte balance was maintained.

At 2 p.m. she complained—for the first time since admission—of abdominal pain, which gradually became more severe and was localized to the right hypochondrium. Examination revealed a rigid abdomen, and preparations were made for immediate laparotomy. At operation an acute perforation was found in the anterior wall of the first part of the duodenum. There was no evidence of peritonitis, and the perforation was closed without difficulty.

Intramuscular cortisone and corticotrophin replaced prednisolone as soon as the abdominal symptoms began, and were continued during and after operation. The dosage was then gradually reduced and steroid therapy was stopped 21 days post-operatively, when an uneventful recovery had been completed. An ulcer regime was maintained for the next two months, and, as the patient remained symptomless, a return to full diet was then allowed. At the time of writing she was still in hospital awaiting an operation for excision of the femoral head, and unfortunately there had been a reactivation of the rheumatoid disease.

COMMENT

It is interesting to note that in this case and in the one reported by Fentress *et al.* (1956) the suppression of clinical signs and symptoms, usually anticipated with the use of steroid therapy, did not occur.

Herzog *et al.* (1955) have shown by biological experiments on animals, and Bunim *et al.* (1955) by clinical assessment, that these new steroids have three to four times the potency of the older corticosteroids. It would appear from recent reports that the incidence of digestive complications is in the same proportion. It is for this reason that many authorities—for example, Boland (1956)—now advise pre-treatment investigation of the gastro-intestinal tract and routine antacids and semi-bland diets.

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Reviews

HUGH OWEN THOMAS

The Life of Hugh Owen Thomas. By David Le Vay, M.S., F.R.C.S. (Pp. 135+vii; illustrated. 25s.) Edinburgh and London: E. and S. Livingstone Ltd. 1956.

It is interesting to find Hugh Owen Thomas among the first few biographies, which include those of Lister and Hunter, so ably published by E. and S. Livingstone, especially as it is not unlikely that only a few have knowledge of Thomas. He was born some years after Lister and before Victoria ascended the throne; he started practice before the establishment of the *Medical Register*. The author has studied the writings of Thomas and much that has been written of him, and presented a "Life" which is built up around his work. His graphic description portrays the figure of the man and a personality agreeing well with what has been told and written by Robert Jones and T. P. McMurray.

The author invites the reader to consider who influenced this able and unusual man in his work. Was it his father, who had the reputation of a successful bonesetter, or Syme or Brodie or Hilton? The reader will realize that Thomas had no hospital appointment, but it is made clear that his services to patients undoubtedly overshadow any ability he may have had of imparting knowledge to colleagues and students. However, we are told that his influence on Ridlon (and so on American orthopaedic surgery) and on Robert Jones has been of the greatest importance, so it would be interesting to read more of the association between uncle and nephew. Too little is told us in this "Life" of what has been given to us by Thomas. Tests and splints associated with his name are not all he has left to us. The author does not indicate whether he expects the reader to consider Thomas a genius and a great man, or whether circumstances or lack of these influenced his life. We are not told if there is evidence that he helped mankind by special skill and original methods. There seems little doubt that his work has been of benefit alike to surgeon and patient since his time, partly through the teaching of Robert Jones, who also was responsible for the provision of the Thomas thigh splint to the Services in the war of 1914–18, after the monstrous loss of life and limb resulting from wounds of the thigh.

The study of the life of Hugh Owen Thomas is a lesson to all surgeons, and will interest the lay reader. This book would be enjoyed by those visiting Liverpool.

ST. J. D. BUXTON.

PARASITOLOGY

Parasites and Parasitism. By Thomas W. M. Cameron. (Pp. 322+xix; illustrated. 35s.) London: Methuen and Co. Ltd. New York: John Wiley and Sons Inc. 1956.

This is one of the most original books on parasitology to appear in recent years. Unlike the majority, it is less concerned with morphology than with life-cycles, while it hardly touches treatment or prevention, but devotes nearly a third of the text to the relation of the parasite to its host, either in the present or speculatively in the remote past. The biochemistry of many organisms is discussed freely, and this indicates one of the important trends the subject is assuming to-day, not only in the metabolic processes of the parasite but in relation to the immunity reactions in the host. The book is more likely to be useful to the biologist or advanced student than to the medical man or veterinarian seeking information about the diagnosis or treatment of a parasitic infection. In fact, the author makes it clear in the preface that he has tried to avoid the anthropocentric or economic point of view. The subject is considered in three main divisions—the Protista, the lower Metazoa (chiefly the helminths), and the higher Metazoa (including vertebrates such as lampreys and vampires). This part is finely illustrated with line drawings which vividly present life-cycles or the natural history and evolution of the organisms. The author is well known for his work on helminthology, and the sections relating to this subject are masterly. In describing the Protista there are a number of errors and omissions which rather spoil this part of the book—for instance, there is no mention of the occult trypanosomes whose life histories would provide useful confirmation of some of the author's views. Later sections in the book describe briefly the epidemiology of parasites; the index is novel in its inclusion of the definition and origin of the more important terms.

P. C. C. GARNHAM.

ANGIOCARDIOGRAPHY IN CONGENITAL HEART DISEASE

Angiocardiographic Interpretation in Congenital Heart Disease. By Herbert L. Abrams, M.D., and Henry S. Kaplan, M.D. (Pp. 233+viii; illustrated. 95s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1956.

This excellent monograph should prove of great value to radiologists, to whom it can serve as a reference book, and also to cardiologists. It is arranged in two parts. The first part describes the historical background of angiocardiography, the technique, the equipment and media employed, and also the general principles of interpretation. Aortography is also presented. The second part deals in individual sections with each of the congenital abnormalities. In addition to presenting the angiocardiographic features, each section opens with a clear, simple presentation of the chief clinical and pathological features of the relevant condition; there is intelligent and useful reference to the literature, although it is a pity that the tiresome numeral system is used and not the Harvard system. It is this inclusion of a simple clinical introduction to each condition which should prove of great help to those who are not fully experienced in congenital heart cases. The illustrations are abundant (161 figures) and well produced. The only criticism is that rather too much is read into some of the postero-anterior views. Perhaps these less satisfactory illustrations will be replaced by better ones in a later edition.

The monograph can be thoroughly recommended.

RUSSELL BROCK.

The *Handbook of Medical Library Practice* (2nd ed., Chicago, American Library Association, 1956) is a comprehensive guide through the intricacies of medical literature which is invaluable to medical librarians and others responsible for its collection, care, and accessibility. It provides information on library methods and services, on bibliographical tools, and on the historical aspects of medicine. It contains chapters on organization and administration, professional training and qualifications of medical librarians, classification, cataloguing, photoduplication methods, reference and bibliographical services, and rare books, and concludes with a valuable annotated bibliography of 1,965 reference works and histories in medical and related fields. The *Handbook* is the work of a team of American medical librarians under the editorship of Miss Janet Doe and Miss Mary Louise Marshall, and is obtainable in this country from the Woolston Book Co., Gamble Street, Nottingham, price 80s.

The *Medical Annual* for 1956 (John Wright and Sons Ltd., 38s. 6d.) is the 74th consecutive issue of this compact and informative yearbook. Its popularity is fully deserved, for the editors, Sir Henry Tidy and Professor R. Milnes Walker, obtain from their distinguished team of contributors a well-balanced review of progress in nearly every field of medicine, including even "Legal Decisions and Legislation." None of the important medical topics of the day are neglected, and there are authoritative contributions on such subjects as the treatment of advanced cancer, the hormone treatment of cancer, the status of cortisone, the surgery of the heart and great vessels, and the chronic rheumatic diseases. A survey of the work on otosclerosis during the last 20 years is particularly useful. When it comes to new drugs, even a yearbook cannot keep up with the output of the pharmaceutical industry, and the fact that the *Medical Annual* for 1956 does not mention the latest "tranquillizing" drugs (though there are useful paragraphs on chlorpromazine and reserpine) shows how little time there is for judicious appraisal of new remedies before they come into general use.

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PATHOGENESIS OF RHEUMATIC ENDOCARDITIS

It is gratifying to see a pathological problem simplified by the discovery of new information, and this seems to have happened with rheumatic endocarditis. Hitherto it has been assumed that two different processes play a part in this condition, one in the early acute stage and the other in the chronic. Now it seems that the same process may account for both. This is indeed a simplification, for, while it is easy to see how the vegetations of acute rheumatism are produced by the deposition of blood platelets and fibrin on the valves, it is not so easy to accept the orthodox view that chronic thickening and stenosis are produced by inflammation, especially as the signs of inflammation are so hard to find. F. R. Magarey[1] has provided, on the lines of the thrombosis hypothesis, what seems a more likely explanation by showing how valvular thickenings can be produced by the organization of fibrin deposits, and his observations have now been confirmed by P. S. Tweedy.[2]

The thrombosis hypothesis dates from a time when the microscope had hardly begun to influence pathology. C. von Rokitansky, the great Viennese morbid anatomist of the last century, described atheroma of the aorta as a deposition of fibrin on the internal surface of the vessel, with subsequent change of the fibrin into fibrous tissue. The microscopists rejected this hypothesis on the grounds that the fibrous thickenings in atheroma were under the endothelium and therefore in the vessel wall rather than on the surface. Virchow described them as reactive overgrowths of the intimal fibrous tissue, and this was the accepted teaching for the next hundred years until the thrombosis hypothesis was revived by J. B. Duguid.[3–5] He showed that when a mural thrombus forms in a blood vessel it becomes covered with endothelium and is thus incorporated in the vessel wall, so that when subsequently organized it forms a fibrous thickening of the intima. The endothelium, according to him, is an adjustable membrane and cannot therefore be taken as a fixed landmark by which developmental relationships can be determined.

Duguid's findings have been confirmed by other workers,[6–9] and now the same principle has been applied by both Magarey and Tweedy to interpreting chronic endocarditis. Magarey showed that when fibrin is deposited on the heart valves it undergoes organization and is converted into fibrous tissue, which becomes incorporated in the valve substance and so adds to its thickness. He also showed how deposits at the junctions of the cusps form adhesions between them and thus narrow the valve orifices. He has thus not only brought the theory of chronic endocarditis into line with that of acute, but has also given a convincing explanation of valvular stenosis.

It may seem hard to believe that so simple a process could have remained so long unrecognized, but histologists have had as a rule to take appearances at their face value. When fibrin is fully organized it is no longer identifiable as such but looks like any mass of fibrous tissue, and when it is incorporated in a heart valve it merges with the original fibrous structure so as to be practically indistinguishable. Thus, unless the histologist is prepared to use imagination—an exercise not always encouraged in his line of work—he must assume that it is part of the original structure; and should that structure seem to be increased in size he is forced, if he subscribes to the doctrine of cellular pathology, to conclude that there has been an overgrowth of it.

There is, moreover, a further difficulty, in that the transformation of fibrin into fibrous tissue requires intermediate changes that have not yet been assigned their final place in the scheme of histopathology. Most observers, while recognizing the presence of fresh fibrin on the surface of the valves in chronic endocarditis, have directed their attention more to the peculiar hyaline substance which so often appears under the surface, hoping perhaps to find in it the underlying cause of the disease. Sometimes this material clearly shows the staining reactions of fibrin; nevertheless, because it appears to be embedded in the valve, it has been taken to be a kind of degeneration of the collagenous connective tissue of the valve itself. Thus the idea of a "fibrinoid degeneration" of collagen has arisen, and, since the same substance is seen in atheroma and kindred lesions of the arteries, the elaborate concept of the "collagen vascular diseases" with all its manifold implications has been

[1] Magarey, F. R., *British Medical Journal*, 1951, **1**, 856.
[2] Tweedy, P. S., *Brit. Heart J.*, 1956, **18**, 173.
[3] Duguid, J. B., *J. Path. Bact.*, 1946, **58**, 207.
[4] —— ibid., 1948, **60**, 57.
[5] —— *Lancet*, 1952, **2**, 207.
[6] Crawford, T., and Levene, C. I., *J. Path. Bact.*, 1952, **64**, 523.
[7] Geiringer, E., ibid., 1951, **63**, 201.
[8] McLetchie, N. G. B., *Amer. J. Path.*, 1952, **28**, 413.
[9] Morgan, A. D., Thesis (M.D.), 1955, University of Aberdeen.
[10] Harrison, C. V., *J. Path. Bact.*, 1948, **60**, 289.
[11] Heard, B. E., ibid., 1952, **64**, 13.
[12] Williams, G., ibid., 1955, **69**, 199.
[13] Levene, C. I., *Lancet*, 1955, **2**, 1216.
[14] Still, W. J. S., and Boult, E. H., 1956, ibid. **2**, 117.

built up. Both Magarey and Tweedy, however, with one accord identify the substance in question as incompletely organized fibrin deposit, and now Tweedy seeks to shake the whole edifice by suggesting that the so-called fibrinoid degeneration is a superfluous concept.

These revolutionary ideas are not founded merely on the imagination of one or two histologists. The principle of the incorporation of fibrin deposits in the vascular system is well established on experimental evidence. C. V. Harrison,[10] B. E. Heard,[11] and N. G. B. McLetchie[8] have shown that particles of fibrin introduced into the veins of rabbits lodge in the pulmonary arteries and are converted into fibrous thickenings of the intima bearing no resemblance to fibrin. Moreover, G. Williams,[12] in a study of experimentally produced arterial thrombi, has shown that before organization occurs there is a stage in which the fibrin becomes condensed and assumes that hyaline appearance we have been taught to look on as a collagen degeneration. It is possible, therefore, that the concept of collagen diseases is based on a wrong interpretation.

How unsafe it is to take histological appearances at their face value has been brought out most strikingly by some recent electron-microscopic studies. C. I. Levene[13] has found that fibres from the surface layers of atheromatous plaques, despite their collagenous appearance, have the electron-microscopic pattern of fibrin, and W. J. S. Still and E. H. Boult[14] have found that the same applies to the surface layers of endocardial fibro-elastosis. Thus even when organization appears to be complete the histology may still be deceptive, and substances which by staining methods are identifiable as one form of tissue may be quite another. If these findings are confirmed, we shall have to admit the existence of an additional form of connective tissue—a fibrous tissue composed not of collagen but of fibrin, and derived not from fibroblasts or any other connective tissue cells but from fibrinogen of the circulating blood.

LIVING WITH A COLOSTOMY

During the past few years a large general hospital serving a medium-sized city and its surrounding villages has been carrying out approximately 50 colostomies annually. As the population at risk is about 250,000 people it might reasonably be inferred that the number of colostomy operations carried out each year in Great Britain is of the order of 10,000. Most of them are permanent, being commonly done as part of the surgical treatment of carcinoma of the rectum and lower colon. The prognosis for most of these patients is good, but since they are often middle-aged or elderly their natural expectation of life is not long. The figure of 10,000 colostomies carried out annually therefore agrees fairly well with the statement[1] that there are more than 100,000 patients with a permanent colostomy in Great Britain—enough to populate a good-sized town. How do these people fare for the rest of their lives ?

The possession of a colostomy used to be regarded as a very serious handicap. It was usual for the surgeon to advise that the colon be regularly washed out each day with warm water, and the patient was commonly hung about with more or less complicated pieces of apparatus requiring cleaning and manipulation. In 1945 W. B. Gabriel[2] opposed the regime of daily wash-outs on the grounds that they were unnecessary, harmful, and dangerous : they were unnecessary because colostomies would usually function regularly once or twice a day with proper training and attention to diet ; harmful because the irrigation of liquids into the colon irritated the mucosa and set up a condition like mucous colitis ; and dangerous to life because of the risk of perforation of the colon. He had collected nine cases of perforated colon due to colostomy wash-outs, and of these eight had proved fatal. A little later C. E. Dukes[3] gave his views on the management of a permanent colostomy after visiting 100 patients in their own homes. He found that about one-third of the patients continued to give themselves a daily wash-out because they had been told to do so, and about two-thirds had either never washed out the colostomy or had given up the practice some years before. Both groups were in good general health. He concluded that daily colostomy wash-outs were unnecessary for most patients and that less inconvenience was caused if the patient could train his colostomy to act naturally.

E. Clayton-Jones[1] likewise advocates training the bowel to act at regular times, pointing out that colonic irrigation is impracticable without adequate facilities —"What may be a simple operation in Mayfair could be impossible in the Gorbals." He gives some practical hints on the care of permanent colostomies. Different diets have to be tried until a formed stool is produced, which usually means avoiding fruit with pips and other coarse roughage and being moderate in the consumption of green vegetables and fruit generally. Another useful measure is to take by

[1] Clayton-Jones, E., *Med. Press*, 1956, **235**, 551.
[2] Gabriel, W. B., *Proc. Roy. Soc. Med.*, 1945, **38**, 692.
[3] Dukes, C. E., *Lancet*, 1947, **2**, 12.
[4] Brooke, B. N., *Postgrad. med. J.*, 1954, **30**, 237.
[5] Benjamin, D., *Amer. J. Surg.*, 1954, **87**, 127.
[6] Hurwitz, A., and Alderman, D. B., *New Engl. J. Med.*, 1953, **249**, 410.
[7] Kaufman, P. A., and Swerdlow, H., *A.M.A. Arch. Surg.*, 1953, **67**, 612.
[8] Hoffman, E., and Macht, A., *Amer. J. Surg.*, 1954, **87**, 140.
[9] Dyk, R. B., and Sutherland, A. M., *Cancer*, 1956, **9**, 123.
[10] Lyons, A. S., *Amer. J. digest. Dis.*, 1956, New Se.ies **1**, 79.

mouth regularly an agent which retains water and thus renders the stool soft but formed. Various preparations of vegetable origin, such as karaya gum, agar, and psyllium seeds, have been used, but Clayton-Jones prefers the use of methylcellulose in the form of granules. Methylcellulose is a synthetic product, unabsorbed by the intestine, and it forms a smooth gel with water. According to Clayton-Jones it has the additional valuable property in relation to a colostomy of being a deodorant, and if the recommended routine is followed he suggests that the number of motions passed can be limited to one before breakfast and perhaps another in the evening. An alternative to methylcellulose is a mixture of kaolin and activated charcoal in the form of granules. Some patients find that taking generous quantities of this by mouth will render the stool well formed and odourless. There is clearly scope for individual trial and error in these methods of gaining control of the colostomy and eliminating faeculent gases, so that there need be no limitation of ordinary social activities.

Provided full control of the colostomy has been achieved, the dressings required are simple. It is enough to cover the colostomy with a piece of gauze or linen smeared with petroleum jelly and to place over this a good-sized square of absorbent cellulose wadding or cotton-wool, which is held in place by a colostomy belt or by a "roll-on" or ordinary corset. If necessary a disk of cardboard or of plastic may be worn under the belt to give added support. At night a wide elastic bandage to hold the dressing in place is sufficient. Whenever the dressings are changed the skin round the colostomy should be cleaned with warm soapy water and then dried thoroughly.

Diarrhoea from a colostomy is a troublesome complication. In a patient who is normally regular a bout of diarrhoea may be checked by giving such drugs as aspirin, amphetamine sulphate, or kaolin combined with an opiate. Opiates should not be given for more than a few days on end for fear of addiction. If diarrhoea persists a full investigation must be made, for, as B. N. Brooke[4] has pointed out, there may be some underlying disease such as regional ileitis which is causing the symptom. Some patients almost inevitably suffer from "wet colostomies" if it has been necessary to make the artificial anus in the proximal part of the colon, but fortunately they are in the minority: for them the introduction of disposable plastic bags has been a great convenience.

There are still many surgeons who prefer to train their patients to wash out their colostomy daily, believing that if the colon is well emptied in the morning the passing of a motion is less likely during the rest of the day. D. Benjamin[5] includes complete and regular cleansing of the large bowel as one essential feature in a "triad of colostomy care," and A. Hurwitz and D. B. Alderman[6] also assume irrigation of the colostomy to be usual; they describe a special apparatus for this purpose which is inexpensive, easy to clean, and leak-proof. How much time can be spent over the process of a daily irrigation can be gauged from their own words: "Most patients employ two 1-litre irrigations and require about 45 minutes for the entire process." While irrigation of the colon continues to be practised there will be the occasional fatality from perforation of the bowel, although this risk can be minimized by inserting into the colon only tubes made of some soft and pliable material and by not irrigating at a high pressure. P. A. Kaufman and H. Swerdlow[7] have reported two cases of colonic rupture after an enema through a colostomy, one of which was fatal, and they review other cases previously reported. E. Hoffman and A. Macht[8] have reported two further cases: both patients recovered with prompt surgical treatment.

It is not merely the correct mechanical functioning of the colostomy which should engage the surgeon or physician who is caring for these patients. The idea of an artificial anus provokes instinctive disgust, and frank explanation and discussion are necessary before the operation, unless this is being done as an emergency. "Even those patients for whom an artificial anus is expected to be only temporary will be shocked by its revelation on the abdominal wall postoperatively unless they have received a previous warning."[4] Thereafter they need instruction in diet and in the care of the colostomy—instruction which is usually well given in hospitals. It is when the patients go home that they often run into difficulties. A recent article by Ruth B. Dyk and A. M. Sutherland[9] on the adaptation of other members of the family to the patient with a colostomy makes it plain that a patient who goes home to a sympathetic and understanding atmosphere is indeed fortunate: details given in this paper provide support to the view that whenever possible daily irrigation should be avoided and "natural" regulation of the colostomy achieved, but the authors do not discuss this aspect of their data, for in common with most other American workers they appear to accept as inevitable the tyranny of the douche-can. For example, A. S. Lyons[10] states: "An occasional patient can be found who has a spontaneous evacuation once or twice daily without irrigation, but I do not believe it to be wise to expect this set of circumstances except in relatively rare instances."

The ideal specification for a permanent colostomy can be summarized shortly: it acts "naturally"

morning and evening at well-regulated times; it requires the minimum of attention in the form of dressings and toilet; and the patient is able to carry out his normal job, live happily in his family, and enjoy his usual recreation. Fortunately, with the help of their medical advisers many patients are able to attain this ideal.

FATAL REACTIONS TO LOCAL ANAESTHETICS

Idiosyncrasy to local anaesthetic drugs resulting in a severe anaphylactic type of response and death is extremely rare.[1] That such a reaction is due to idiosyncrasy can be accepted only when it follows an exceedingly small amount of the drug. Sudden death within a few seconds of the topical application of a small dose of cocaine may be due to a direct action on the heart, causing ventricular fibrillation, but the unique pharmacological properties of cocaine—sympathomimetic and adrenaline-potentiating—imply that such a reaction would be peculiar to this agent. Such dramatic and unpredictable fatalities are fortunately rare, and with the justifiably diminishing use of cocaine should soon not occur at all. Most fatal reactions to local anaesthesia, as to general anaesthesia,[2 3] are the result of faulty technique.

The usual type takes the form of convulsions followed by respiratory and finally circulatory failure. Premonitory signs include pallor, apprehension, and restlessness. Treatment to control the convulsions (for example, by a small dose of intravenous barbiturate or relaxant), artificial respiration with oxygen to prevent anoxia, and thereafter support of the circulation should prevent a fatal outcome if instituted in time. The heart may stop owing to anoxia or to the direct toxic effect of the drug. In this event cardiac massage must be undertaken without delay.

The occurrence of such reactions depends on the toxic threshold of the drug and on the factors which lead to a blood concentration above this level in the patient. The reaction threshold may vary in a given patient from time to time, according to nutritional state, the effect of premedication, and other factors. It is low in drugs with a high inherent toxicity; cocaine and many of the more potent compounds fall into this class, and it is perhaps wise to avoid using them whenever a safer drug will give an equally satisfactory clinical result. The blood concentration attained in the patient depends on the rapidity of entry into the blood stream and on the rate of concurrent elimination or destruction of the drug. Cocaine is detoxified more slowly than many synthetic local anaesthetics, another factor reducing its safety.

Inadvertent intravenous injection, overdosage, and giving unnecessarily high concentrations of local anaesthetics all lead to high blood levels, with the danger of toxic effects. Drugs such as procaine and lignocaine are commonly dispensed in 2% concentration and often given in that strength for infiltration (more than 30 ml. of this strength would constitute an overdose in most patients); with either agent ½–1% concentration would be adequate for most purposes and is preferable for safety. Adrenaline is often included in solutions of local anaesthetics, since it retards absorption into the blood stream and prolongs the anaesthetic effect; but dangerous and even fatal results have followed excessive amounts of adrenaline given in this way, and the dosage needs to be carefully checked.

Many of the reported fatal reactions follow the topical application of local anaesthetic agents. In part this is because the more toxic agents are the more effectual for this purpose and because relatively high concentrations are used. For example, only 1 ml. of 10% cocaine contains 100 mg., which amount is regarded as the maximum permissible for topical application. Again, topical application of a local anaesthetic solution to the mucous membrane of the respiratory tract can result in rapid absorption of the drug, leading to a high blood level. The exceedingly rapid absorption of fluids injected into the respiratory tree was reported a century ago[4]; the rate of entry to the blood stream may approximate to that of direct intravenous injection. J. E. Steinhaus[5] has confirmed this experimentally by spraying local anaesthetics down the tracheas of rabbits. Doses thus have to be small, and drugs with the least possible toxicity are best given. 1 ml. of 2% amethocaine contains 20 mg., and the drug is about ten times more toxic than procaine after intravenous injection. A number of fatalities, one recently reported,[6] have followed the topical application of 2% amethocaine to the respiratory tree. D. C. Moore and J. Green[1] suggest that the dosage should be restricted to 40 mg. and that it should be used as a 0.5% aqueous solution; a total dose of 8 ml. is regarded as the maximum permissible for topical anaesthesia of the larynx and tracheobronchial tree. They state that this strength is adequate for satisfactory anaesthesia. Lignocaine in 2–4% concentration is a highly efficient surface anaesthetic, and its toxicity is only slightly greater than that of procaine (for instance, 0.5% lignocaine can be administered intravenously for various therapeutic purposes in a similar fashion to procaine solutions). If this or similarly safe agents[7] supplanted the more toxic drugs for topical anaesthesia many fatal reactions would probably be averted.

MUMPS ORCHITIS

The importance of mumps lies mainly in its complications, of which epididymo-orchitis is the most frequent and the most severe. It affects young adult males, being very rare before the age of puberty.[1] It causes severe pain, is always accompanied by pyrexia, and often by prostration or even delirium. It may lead to partial atrophy of the testicle and sub-fertility, though the evidence for this is not very convincing, and most

[1] Moore, D. C., and Green, J., *Calif. Med.*, 1956, **85**, 70.
[2] Edwards, G., Morton, H. J. V., Pask, E. A., and Wylie, W. D., *Anaesthesia*, 1956, **11**, 194.
[3] *British Medical Journal*, 1956, **2**, 868.
[4] Colin, G., *Traité de physiologie comparée*, Baillière, Paris, 1856, **2**, 39–41.
[5] Steinhaus, J. E., *Anesthesiology*, 1952, **13**, 577.
[6] Adriani, J., and Campbell, D., *J. Amer. med. Ass.*, 1956, **162**, 1527.
[7] Harris, L. C., Parry, J. C., and Greifenstein, F. E., *Anesthesiology*, 1956, **17**, 648.

clinicians will know of patients who have proved fertile after unilateral and even bilateral orchitis due to mumps. It is nevertheless a very disabling complication while it lasts and hitherto has not responded readily to treatment. Several reports now suggest that the use of corticotrophin or cortisone may be worth further study.

L. Martoni[2] reports excellent results in three cases. Hydrocortisone was given orally in doses of 125 mg. the first day, followed by 100 mg., 75 mg., and 50 mg. on the next three days. Pain was relieved and the temperature fell in 24 hours, and the swelling and tenderness subsided in two days. Examination 20 to 25 days later revealed no sign of atrophy. J. H. Solem[3] treated two severe cases with 100 I.U. of long-acting corticotrophin. Both had had orchitis for several days before treatment and in both cases tenderness and swelling subsided within 24 hours. One of these patients had a recrudescence of the orchitis, which a second injection promptly controlled. A. G. Bower[4] gives no figures or case histories but claims that cortisone by mouth in an initial dose of 300 mg. followed by 100-mg. doses every six to eight hours for two to four days caused diminution of pain in six to twelve hours and subsidence of swelling in two to four days. He claims that the initial dose should be at least 300 mg. by mouth. G. C. Risman[5] is less enthusiastic. He gave cortisone to five patients in doses of 75 mg. every six hours for one day, followed by 50 mg. every six hours for three days, and then smaller doses for three to six days more. In all of five patients pain was relieved within 24 hours, but the fever and the swelling were not affected. In three patients swelling of the other testicle developed during treatment, but the swelling and duration of symptoms were milder. In one patient, who had both testes affected at the same time, one increased in size during treatment but responded rapidly to increased dosage. It is evident that the claims of different authors vary considerably, though all claim some improvement. Details of dosage and time of administration need further study, and the treatment cannot be accurately assessed until many more cases have received it.

TORULOSIS AND HODGKIN'S DISEASE

Torulosis is a systemic fungal disease caused by a yeast-like organism now known as *Cryptococcus neoformans*. The first description of the disease was that of O. Busse and A. Buschke in 1895,[6] and cases have been reported in small numbers since then. B. R. Gendel, M. Ende, and S. L. Norman[7] referred in 1950 to a total of 165 cases, and in 1951 V. P. Collins, A. Gellhorn, and J. R. Trimble[8] mentioned 241 cases. The causal organism has been isolated from soil, as have the organisms of certain other systemic mycoses, and it appears to have a saprophytic role in nature. The commonest site of human lesions is the central nervous system, which is involved in about 80% of patients with the disease. In these cases the subarachnoid space is seen at necropsy to be characteristically distended by gelatinous material, and often small cysts containing the cryptococci are present in the cerebral substance. Clinically the condition is manifested by a meningo-encephalitis, and cryptococci can often be recovered from the cerebrospinal fluid. The next most common site of disease is the lung, which is believed to be the usual portal of entry of the infection. Again, gelatinous lesions may be found there, or sometimes the lesions are granulomatous. Dissemination may take place, and then lesions will be found in many organs, including lymph nodes. The skin may ulcerate, and cryptococci can sometimes be isolated from the fluid which exudes from the lesions.

In 1923 W. Freeman and F. D. Weidman[9] reported a case in which torulosis and Hodgkin's disease were believed to coexist in the same patient, and since then the apparent association of the two diseases has received some attention. Gendel and colleagues[7] referred to 14 cases in which the two diseases were believed to be present in the same patient, though the number may be no more than 11 if cases are excluded in which the evidence for both torulosis and Hodgkin's disease is perhaps open to question.[8] More recently further cases in which cryptococci were found and the histological findings supported a diagnosis of Hodgkin's disease have been described.[10–12] The association between cryptococcal infection and a form of lymphadenopathy closely resembling, or even identical with, Hodgkin's disease seems to be proved, for it occurs too often to be a matter of chance. But that cryptococcal infection is the specific cause of Hodgkin's disease is out of the question: many cases of cryptococcal infection are known in which there is no evidence of Hodgkin's disease, and in the great majority of cases of Hodgkin's disease there is no evidence of cryptococcal infection. In animal experiments, too, no lesions resembling those of Hodgkin's disease have been produced by infection with cryptococci. Two possible explanations of this association have been considered—first, that cryptococcal infection can produce a granulomatous type of tissue reaction which is similar to that of Hodgkin's disease, and secondly that infection with cryptococci is a late event and occurs as a complication of Hodgkin's disease. It is at present not possible to decide between these two views with certainty. In support of the first is the fact that infection with cryptococci has been found in association not only with Hodgkin's disease but also with other types of

[1] See *British Medical Journal*, 1954, **2**, 1343.
[2] Martoni, L., *Clin. pediat.* (*Bologna*), 1955, **37**, 402, abstr. in *Amer. J. Dis. Child.*, 1956, **91**, 390.
[3] Solem, J. H., *Lancet*, 1953, **2**, 453.
[4] Bower, A. G., *J. Amer. med. Ass.*, 1956, **162**, 425.
[5] Risman, G. C., ibid., 1956, **162**, 875.
[6] Busse, O., and Buschke, A., *Dtsch. med. Wschr.*, 1895, **21**, Vereins-Beilage, 14.
[7] Gendel, B. R., Ende, M., and Norman, S. L., *Amer. J. Med.*, 1950, **9**, 343.
[8] Collins, V. P., Gellhorn, A., and Trimble, J. R., *Cancer*, 1951, **4**, 883.
[9] Freeman, W., and Weidman, F. D., *Arch. Neurol. Psychiat.* (*Chicago*), 1923, **9**, 589.
[10] Symmers, W. St. C., *Lancet*, 1953, **2**, 1068.
[11] Misch, K. A., *J. clin. Path.*, 1955, **8**, 207.
[12] Levene, M., and Michaels, L., ibid., 1955, **8**, 201.
[13] Gordon, M. H., in *Rose Research on Lymphadenoma*, 1932, Bristol.
[14] Beck, A., Hutchings, M. W., Makey, A. R., and Tuck, I. M., *Lancet*, 1955, **1**, 535.
[15] Dubin, I. N., *Ann. intern. Med.*, 1947, **27**, 898.
[16] Benham, R. W., *J. infect. Dis.*, 1935, **57**, 255.

lymphadenopathy.[8] In some cases the diagnosis of a specific lymph-node lesion was considered to be established, and this group includes Hodgkin's disease, lymphosarcoma, and leukaemia. In others the histology of the lymph nodes varied. A further point in support of this view is that cryptococci have sometimes been recovered from the glands of patients with Hodgkin's disease in whom there was no clinical evidence of torulosis[13] and from stomach washings in such a patient.[8] One difficulty in accepting this view is that in most cases in which the diseases are believed to coexist either the cryptococci are not recovered at all from sites where the tissue changes are those of Hodgkin's disease or, if present, they are so only in small numbers.[10 12 14] In support of the other view, that cryptococcal infection is a late event in cases of Hodgkin's disease, there is a certain amount of indirect evidence. I. N. Dubin[15] has found that patients with Hodgkin's disease have a generally poor immunological response to infection, and M. Levene and L. Michaels[12] point out that many organisms such as diphtheroid bacilli, avian tubercle bacilli, and *Brucella* can be secondary invaders in Hodgkin's disease. R. W. Benham[16] reported that cryptococci can be recovered from the skin of normal subjects, and these might well become established in the body if the immunological response of a patient was poor. That there is an association between torulosis and a lymphadenopathy closely resembling Hodgkin's disease, an association occurring too frequently to be explicable by chance, seems proved. But at present it does not seem possible to decide whether the cryptococci known to cause torulosis can cause this and other reactions of lymphoid tissue or whether they appear late on the scene as secondary invaders in patients whose immunological response to infection is impaired.

NOMENCLATURE OF BLOOD-CLOTTING FACTORS

The object of nomenclature is presumably to facilitate the interchange of knowledge, and yet there can be few fields of research where it is causing more confusion and misunderstanding than that of blood coagulation: clotting factors are known by different names not only from country to country but within single countries and from laboratory to laboratory. It is not surprising that many clinicians find the whole subject baffling. The classical theory of blood coagulation postulated certain factors, and there is widespread agreement on the meaning of the terms prothrombin, thrombin, fibrinogen, fibrin, and calcium, though thromboplastin is less clearly understood than the others. But there are at least four additional factors which appear to be important in the phenomenon of clotting, and each of these four has received a variety of names. To give an example of the confusion which exists, one of these substances has been described as Factor VII, proconvertin, serum-prothrombin-conversion accelerator, stable factor, autoprothrombin I, serozyme, kappa factor, prothrombinogen, co-thromboplastin, serum accelerator, prothrombin conversion factor, and the prothrombin converting factor. As a result, communication between English-speaking workers has been definitely retarded, and for those who do not read English the possibility of misunderstanding is even more serious. In addition, substances of platelet origin and blood-clotting inhibitors are now being studied in detail and new names are being proposed for these.

Realizing the harmfulness of this confusion, a number of the leading workers in this field decided at the First International Congress on Thrombosis and Embolism in Basle that it was their responsibility to try to reach some agreement on nomenclature, and they therefore set up a committee to determine whether it would be possible to introduce a standardized nomenclature for those factors which are generally agreed to play a part in the physiological clotting of blood. The committee had a further meeting during the Sixth International Congress on Haematology at Boston last August, when the membership was further increased and a number of working parties were given the task of collecting the evidence in favour of the different blood-coagulation factors and of suggesting some neutral nomenclature which might be intelligible to medical practitioners whatever the country they lived in. The task confronting the committee presents very real difficulties, because with few notable exceptions the factors thought to be concerned in normal blood coagulation have not been isolated and identified. The committee wisely determined that any nomenclature selected as an international one should not be tied to any theory of coagulation, since the constant changing of theories has in the past led to repeated changes of terminology. It was also agreed that the existing terms prothrombin, thrombin, fibrinogen, fibrin, and calcium, being already used in most countries, should not be changed; that, for the reasons given above, any provisional terminology should not imply any supposed function or constitution of the factor to which it refers; and that international terms should be short, simple, and readily understood by people of different nationalities. Probably a common symbol, either a name or a number, will be selected for each factor, and each author will be encouraged to use this together with such a synonym as he may wish to use, the international symbol to be in brackets.

The work of the committee cannot reach fruition without the collaboration of different scientific societies in Europe and America, and it is hoped that the European and American societies of physiology, haematology, clinical pathology and so on will be willing to assist the committee in its endeavours, and, if they or their individual members have views they wish to put forward on the question of nomenclature of blood-clotting factors, that they will communicate with the secretary of the international committee, who is Dr. M. Verstraete, Cliniques Universitaires Maladies Internes B, Laboratoire de Physiopathologie, 57, Kapucijnenvoer, Louvain, Belgium. Thus by international collaboration it is hoped to achieve a nomenclature which will be workable and to get rid of much of the confusion which exists at the present time.

Nova et Vetera

ISAAC BUXTON (1773–1825)

"ON THE USE OF A REGULATED TEMPERATURE IN WINTER COUGH": A CONTRIBUTION TO THE HISTORY OF CHRONIC BRONCHITIS

BY

V. C. MEDVEI, M.D., M.R.C.P.

The combined meeting of the Sections of Pathology and Epidemiology of the Royal Society of Medicine on February 21, 1956, dealt in an admirable manner with problems of the epidemiology, bacteriology, and morbid anatomy of chronic bronchitis. It was pointed out that North-Western Europe seems to show a greater prevalence than the rest of the Continent, with England and Wales in the lead. A number of factors responsible for the origin were mentioned, such as respiratory infection, air pollution, type of bacteria (allergic), sensitivity of the mucous membranes, cigarette smoking, and several others.

In the discussion which followed, somebody asked if temperature studies had been made, taking into account the rapid change of climatic conditions even within a restricted area, such as a district of London, which may occur within a few hours, or even an hour: the transition from severe frost in the early morning and a snowstorm between 8 and 8.30 a.m. to sunshine and thawing conditions an hour later is a quite common experience. Such studies have apparently been carried out abroad ("microclimatology"), and seem also to have taken into account conditions of internal heating, windows, ventilation, and allied problems; from the reply given it seems that there is no similar study in existence in this country.

The problem is not new. The question of regulated temperature in relation to winter cough and consumption was described in detail by Isaac Buxton, M.D., Physician to the London Hospital and Surrey Dispensary in 1810.

Norah Schuster, in her paper on Buxton (*Proc. roy. Soc. Med.*, 1955, **48**, 326), mentions this essay, but refers mainly to his enthusiasm concerning the heating and ventilation of sick-rooms.

Isaac Buxton was born on May 6, 1773, in Grange Walk, Bermondsey. At 9 years of age he went to St. Paul's School as a Foundation Scholar. About his later youth up to 1800 little is known. In that year he went to Göttingen to study medicine. In 1802 he wrote his thesis and obtained his doctorate. He then returned to London and became a pupil dresser to Astley Cooper at Guy's, and in 1805 obtained the Licence of the Royal College of Physicians. A year later we find him on the staff of the Surrey Dispensary, and after some fight he was elected to the staff of the London Hospital in 1807. During the following period of increasing practice he married Janet Travers, a cousin of the surgeon Benjamin Travers. Whether he ever used a stethoscope is not known, but he might have known it when he retired in 1822. He understood French and had read Laennec, so it was possible that the use of the stethoscope was quite familiar to him. He was elected to the Council of the Hunterian Society, but his health began to fail. In 1822 he resigned from the London Hospital on grounds of ill-health. Three years later he died in Camberwell and was buried in Bunhill Fields, and, as Norah Schuster says, "has rested in obscurity ever since."

Apart from the above-mentioned essay, he seems to have been fascinated by the possibilities of vital statistics, as he studied and wrote up the statistics of London Hospital admissions for 70 years until 1820, offering a most valuable analysis on the nature and spread of outbreaks of fever in the East End in 1817 and 1818.

He was a founder of the infirmary which later became known as the Royal Chest Hospital (in 1814), and where, for the first time, wards were kept at a constant warm temperature, to the great benefit of the poor sufferers from chest disorders. He aimed at a temperature of 60 to 65° F. (15.5 to 18.3° C.) day and night during the winter months. Although the idea was not entirely original, Buxton was one of the first to put it into practice.

The complete title of Buxton's article is: *An Essay on the Use of a Regulated Temperature in Winter-cough and Consumption; including a Comparison of the Different Methods of Producing such a Temperature in the Chambers of Invalids.* It deserves, however, a much more detailed appreciation. The description of winter cough is perfect.

"It is absolutely necessary that I should be more minute in my description of what I mean by 'Winter cough'; because this disease, although perhaps more frequent than consumption, has not been described so often and so minutely; . . . Those who are affected with winter cough, generally feel themselves very well during the warm weather of summer. But, when the winter comes, they are afflicted with severe coughing. This cough is often so extremely troublesome during the night, as almost entirely to deprive them of rest. It is generally brought on with a considerable degree of violence whenever they go out into the cold air; and is easiest during the time of their continuance in a warm room. . . . Their breath is generally extremely short, so short that they frequently walk about with a considerable degree of difficulty; and an exertion rather greater than usual is very severely felt. If they draw in the breath deeply, pain is often occasioned in the chest, together with sudden catching and cough. Tightness across the same part is another symptom which they experience. Patients with this complaint in general expectorate considerably. The expectoration varies much: but, for the most part, it is thick, and large in quantity. . . . Sometimes they spit blood; but the quantity is usually not very large. Their complaints vary in the winter season, according to the state of the weather; so that when the wind is southerly they feel relieved, and when it changes to the north or north-east, every symptom is materially aggravated . . . towards the latter end of winter or beginning of spring they are extremely thin and debilitated. Patients of this description are very liable to take cold; . . . and, when they have caught cold, the cough, the pain, the expectoration, the shortness of breath, and other symptoms, are considerably aggravated.

"As the spring advances, and mild weather comes on, the cough and other affections of the chest gradually abate; till, on the arrival of warm, settled summer weather, it . . . entirely quits them; and probably they enjoy, for a time, the pleasing hope that they are now thoroughly recovered. . . . But the succeeding winter destroys the pleasing delusion. They are again affected with the winter cough; and, if the weather is at all severe, most probably in a greater degree than during the preceding winter. In general the cough and other symptoms of the complaint become worse and worse every succeeding winter; and the remission between the attacks, during the summer, shorter, till at last patients frequently have the cough both winter and summer, although most severely during the winter. . . . The same train of symptoms has had various denominations applied to it. . . . I do not adopt the term chronic catarrh (perhaps the most proper denomination) because, although understood by medical men, it would not be so readily apprehended by others; nor do I employ the word asthma, because I think it better to follow Cullen's* example, and to confine the use of that expression to one particular kind of complaint. Winter cough is not the term I would fix on, were I writing a system of nosology, as I am well aware that it is liable to some objections. But since it is generally adopted in common life, not liable to ambiguity, being intelligible to persons medical and non-medical, and sufficiently designating the disease in question, I thought proper to employ it."

In the next paragraph he discusses the "frequency of winter cough and consumption," based on returns from "authentic documents," such as Dr. Willan's "Reports on the Diseases of London," rather than on "random modes of judging" from his own private practice: another feature which sounds more like present-day methods of studying the problem. In paragraph 4 he talks "of the Fatality of these disorders," and the introductory sentences are again worthy of detailed quotation:

"What renders consumption and winter cough still more worthy of our attention is, the amazing number of persons who fall victims to these complaints. No one will be surprised that

*Dr. Wm. Cullen (1710–90), also quoted by Badham (pp. 20–21 in the 2nd ed.), was Professor of Medicine in Glasgow and Edinburgh.

this is said, relative to consumption. But that an assertion of this kind should be made relative to winter cough, may, at first sight, appear extraordinary. Yet it is a certain fact, that a very considerable proportion of those who are affected with winter cough, ultimately die either of that complaint or of its consequences. . . . Consumption is a disease that kills of itself, i.e., without inducing another disease, which, although a consequence of the first complaint, puts on a particular character. Winter cough superinduces other complaints, which kill the patient; the death is then set down to the latter disorder and not to the winter cough."

In the following paragraph the usual terminations of winter cough are discussed—namely (1) consumption; (2) pneumonia (inflammation of the lungs); (3) dropsy, obviously as an expression of the failing heart; and (4) water in the chest (pleurisy), often in connexion with acute pneumonia.

In paragraph 6 important observations are made on the causation of these complaints:

"It is always of great importance to discover the causes of a complaint, as such discovery may probably lead either to its prevention or cure. . . . We have not to go far to discover the principal causes of consumption and winter cough. I am persuaded they will on examination be found to lie chiefly in the variableness and frequent severity of the climate. . . . When do these diseases make their commencement? Certainly in the severest and most variable weather of winter and spring. . . . If we go into the warm, settled climates, such as Spain, Italy, and the South of France . . . we shall scarcely ever meet with tedious cough and shortness of breath, such as we have described by the name of winter cough. Yet the inhabitants of some of these climates, when removed to England, are still more liable to these diseases than even the natives themselves. . . .

"Exposure to alternations of heat and cold is the common origin of protracted cough and shortness of breath, as well as of consumption. . . . We have before observed, that this winter cough vanishes on the approach of summer, and, could summer be always continued, would never again appear. All this, I think, is abundantly sufficient to prove, that variable and severe weather is materially concerned in producing and supporting by far the greater number of consumptions and protracted coughs."

In this country, Charles Badham (1780–1845) is regarded as the father of bronchitis, because he used the term first. Badham was a scholar and poet, as well as a doctor. He was an M.D. Edinburgh, which degree he obtained in the same year as Buxton did his in Göttingen. He added to it the M.D. Oxford fifteen years later, and was elected F.R.S. and F.R.C.P. in 1818; eventually he became a Censor of the College of Physicians (1821), and professor of physic in Glasgow in 1827. At the time of the first publication of his description of bronchitis, he was physician to the Westminster General Dispensary. He also was a Royal Physician to the Household of the Duke of Sussex. His treatise—which was, incidentally, dedicated to the Duke—was first published in 1808, two years before Buxton's essay. He set to work more methodically than Buxton, in so far as he gave a good historical introduction, and a systemic classification of various types of bronchitis based on punctilious clinical and morbid anatomical observations. He also gave a detailed account of the treatment, and devoted a full chapter to the "History and Treatment of Chronic Coughs, etc." which covers more or less the subject of Buxton's essay. In two respects, however, it seems inferior to Buxton's study. There is no mention of vital statistics to prove the prevalence and mortality of the disease. On the other point, Buxton, who was familiar with Badham's tract, wrote: "Dr. Badham gives his sentiments relative to this treatment of chronic bronchitis—that is, winter cough—in the following terms (Observations on the Inflammatory Affections of the Mucus Membrane of the Bronchiae, p. 122†). 'An uniform moderate temperature, to be secured only by confinement to the house during the unfriendly winters of this climate, is a measure about the propriety of which (where it can be adopted) no person can doubt.' Thus, therefore, both‡ these writers perfectly agree with me as to the propriety of the measure. But neither of them has brought forward any instance where it was used" (pp. 99–100).

Buxton's essay can be regarded as a minor classic. His description of the clinical picture can hardly be bettered; the choice of the name of the disease appears sound; the follow-up, the modes of termination, and the fatality of the illness are better assessed than by Badham. The attempted use of vital statistics shows Buxton at least half a century ahead of his contemporaries.

His real point is that the temperature changes are so rapid and by no means merely seasonal: cold summers, two or three very warm winter months followed by two or three weeks of sharp frost and icy snow blizzards are by no means uncommon; but the main problems are the great *daily* variations of temperature in any given spot—for example, in the heart of London.

The task, therefore, to cope with only one single aspect—although it is an important factor—of the problem of prevention and mitigation of winter cough is a very great one: no wonder it has taken 140 years to appreciate and heed Isaac Buxton's opinion and suggestions. It may take another 50 years before they are fully carried into practice. Isaac Buxton deserves to be remembered when the history of bronchitis is written.

†At page 132 in the second edition, which was entitled *An Essay on Bronchitis*. London, 1814.

‡Dr. Thomas Beddoes (1760–1808), cited by Buxton on page 98.

Reports of Societies

TOXOPLASMOSIS: A WIDESPREAD INFECTION

RECOGNITION AND TRANSMISSION

The Royal Society of Tropical Medicine and Hygiene discussed toxoplasmosis at a meeting on January 17 at Manson House, London. Owing to the increasing number of recorded human infections, especially severe and fatal forms of the congenital disease, much attention has been devoted to *Toxoplasma* in recent years. Infection in man (and animals) has been found in many parts of the world.

Professor P. C. C. GARNHAM (London School of Hygiene and Tropical Medicine) introduced the speakers with the observation that it might be asked why a tropical society should discuss a subject with no special tropical significance. He regretted so little work on the disease had been done in the tropics, and suggested that workers there should look out for more cases, ascertain the incidence in the general population, and define the local animal reservoirs.

Clinical Picture and Incidence

The variety of presentation in human infections was outlined by Professor C. P. BEATTIE (Sheffield). The syndrome in infants might be characterized by internal hydrocephalus or microcephaly, choroidoretinitis, signs of central nervous system involvement, or cerebral calcification. The mortality rate in severe congenital cases was high, and children surviving were usually mentally retarded. At necropsy, distension of the ventricles with yellowish fluid, miliary granulomata, necrosis, and caseation were frequent features, while *Toxoplasma* might be found in the tissues. The disease might be noticed at birth, but could become obvious only days, weeks, or even months later by many signs indicating damage to the nervous and ocular systems. There could be jaundice with a purpuric or maculo-papular rash, enlargement of the liver and spleen, and lymphadenopathy. The frequency of congenital infection was incompletely known. In Britain Professor Beattie put the figure at about 1 in 35,000 live births: from 1950 to the end of 1956 110 cases were diagnosed in children under 5 years in England.

Even with congenital infections, however, severe disease was the exception, said Professor Beattie; and, although in adults acquired disease could be severe, afebrile lymphadenopathy seemed the common mode of presentation.

Surveys indicated that from one- to three-quarters of the populations in different countries possessed antibodies against *Toxoplasma*. Turning to transmission, Professor Beattie suggested that attention should be paid to direct transfer from man to man and to the possible importance of entry via the respiratory tract. He presented figures indicating infection to be commoner in rural areas than in urban localities, and that animal-handlers have a higher infection rate than other occupational groups, as suggested by serological tests. Variation in the virulence of the organism was difficult to explain, but concomitant illness might be important in deciding the severity of the attack.

Serological Tests in Diagnosis

Dr. I. A. B. CATHIE (Hospital for Sick Children, Great Ormond Street) gave the results of investigations on the specificity of the various serological tests for *Toxoplasma*. Several authors had found an unexpectedly high proportion of sera to be positive for the dye test among animals infected with such organisms as *Sarcocystis*, *Trichomonas*, and *Trypanosoma cruzi*. He had been able to substantiate these findings for *Sarcocystis*, but had found that the "toxoplasm-hostile factor" involved could be inactivated by heating at 56° C. He had also shown that properdin did not interfere with the dye test; similarly the results of testing sera from patients with *T. cruzi*, *T. gambiense*, and *Trichomonas* gave no evidence that antibodies affecting the dye test were produced by these organisms. Nor did infection with *Salmonella typhi* or malaria give rise to a positive complement-fixation reaction for toxoplasmosis as reported by some other authors. Dr. Cathie concluded therefore that, so far as the human subject was concerned, the reliability of both the dye test and the complement-fixation test for *Toxoplasma* was upheld. In diagnosis, however, both tests should be used: for example, a dye test of 1:64 with a negative C.F.T. would be of little significance, but an additional C.F.T. titre of 1:16 would be corroborative. From his evidence, Dr. Cathie considered that much experimental work on animals was not applicable to man, at least so far as trichomonad and trypanosome infections and the dye test are concerned.

Animal Reservoirs of Infection

Toxoplasma infection in animals was discussed by Dr. R. LAINSON (London School of Hygiene and Tropical Medicine). Such infections appeared to be world-wide, he said. Whereas no warm-blooded animal species seemed to possess complete natural immunity, it had yet to be proved that cold-blooded animals were infected in nature. It was generally agreed that only a single species of *Toxoplasma* existed.

The study of host reservoirs for human infection was complicated by the extremely wide range of host species and our ignorance of modes of transmission. Among dogs, only about a hundred cases had been reported where the parasite had been demonstrated, although serological evidence suggested that they might often suffer from chronic infections. Cats, too, often showed antibodies against *Toxoplasma*, but there had been few instances of actual isolation. The organism had also been isolated from cattle, pigs, sheep, rabbits, pigeons, and poultry. Infections had been found in wild rats, but the incidence was apparently not high; occasionally house-mice were infected.

Dr. Lainson stressed that the only absolute proof of infection was the isolation of the parasite, and he discussed how this might best be achieved. After intraperitoneal inoculation of brain tissue into mice he had succeeded in isolating *Toxoplasma* from 6 of 113 domestic rabbits, all of 5 members of the Mustelidae (stoat family), and 1 of 99 *Rattus norvegicus*. No infections were found in 122 wild rabbits, 399 house-mice, and 85 birds. He mentioned also the difficulties in detecting avirulent strains of the parasite. Interpreting these findings, Dr. Lainson concluded that *Toxoplasma* was not uncommon in wild and domestic animals, but normally there was a very well-balanced host-parasite relationship. The highly virulent forms of *Toxoplasma* were probably aberrant or altered strains. He thought it possible that humans might become infected through handling raw, infected meat—either through cuts and abrasions on the hands or by direct conveyance of parasites to the mouth. Carnivorous animals seemed to be more commonly infected than omnivores or herbivores, and this suggested oral transmission. Cats and dogs were often fed on raw meat, and might, if they became infected, act as sources of the human disease. In an investigation of London dogs he had found that 42% had antibodies against *Toxoplasma*.

Discussion

Opening the discussion, Dr. J. K. A. BEVERLEY (Sheffield) gave case reports in support of Professor Beattie's suggestion that the visceral stage of congenital infection could be eliminated by passively acquired antibodies. He agreed with Dr. Cathie's views on the specificity of the serological tests for toxoplasmosis, and gave illustrations to support this. As to the significance of antibody titres, he considered a dye-test titre of 1:800 and a C.F.T. titre of 1:16 indicated active or very recent infection, but more significant was a rise in titre between the early stages of infection and convalescence. Low dye-test titres might indicate very recent infections or past subclinical ones; the parasites had been isolated in cases showing such low titres.

With regard to the treatment of toxoplasmosis, Dr. Beverley discussed the action of the following drugs: in mice, sulphonamides, diamino-diphenyl sulphones, and diaminopyridines (all effective); in rabbits, pyrimidine-substituted sulphonamides and diamino-pyrimidines (ineffective) and thiazole-substituted sulphonamides and diphenyl sulphones (both good). In acute human infections there was evidence that sulphadimidine and pyrimethamine were effective. In chronic cases chemotherapy might help by preventing future relapses due to rupture of cysts, but could not help in cases with tissue breakdown due to hypersensitivity. Cortisone was often useful in acute exacerbations.

Professor R. J. V. PULVERTAFT (Westminster Hospital) showed an interesting film of the motility and mode of entry of *Toxoplasma* into the host cells, while Dr. J. D. FULTON (National Institute for Medical Research) described useful methods whereby the parasite might be obtained in pure suspension for biochemical assay. Several other speakers described their experience of cases of congenital toxoplasmosis.

Recently a W.H.O. team visited Austria to advise on the health problems raised by the influx of Hungarian refugees. The team was particularly concerned with the risk of epidemics and the mental health of the refugees. Apart from the immediate effects of their journey—cold and hunger—the team reports that the refugees were, generally speaking, in good physical health. Vaccination programmes in Hungary appeared to have been thorough, particularly against smallpox and diphtheria, and precautions were being taken against outbreaks of typhus. The team emphasizes the importance of understanding the psychological difficulties of the refugee in planning help. In spite of individual differences and variations in the causes of flight, refugees the world over had a number of features in common: they were afraid of what they were fleeing from; their attitude towards rules and regulations had changed because they had had to break rules in order to save their lives; they suffered from some form of home-sickness; and they expected a great deal from the country and the people that received them. Unless the many willing helpers appreciated these things, states the team, disappointment on both sides was inevitable, and disturbances would occur. A typical refugee reaction after the triumph of at last reaching safety was to become completely exhausted, to make no effort at all after the tremendous effort of flight. This should be regarded as a normal reaction. What was needed was human contact: anything that bound the refugee to a society should be encouraged.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Two New Human Genes

SIR,—Your annotation (*Journal*, January 19, p. 154), "Two New Human Genes," on the interesting findings of Allison and McWhirter,[1] conveys the inaccurate impression that the two hypothetical inherited factors "As" and "bt" are well established, like blood antigens or haemoglobin variants. No report about these new factors, based on a large series of families, seems to be available. Moreover, it is not yet known how far the phenomena of beetroot pigment and methane-thiol (methyl mercaptan) excretion are independent of incidental influences, such as rate of absorption from the gut or peculiarities of intestinal flora. Until these matters have been settled it seems premature to discuss the evolutionary significance of the observations.—I am, etc.,

London, W.C.1. L. S. PENROSE.

REFERENCE

[1] Allison, A. C., and McWhirter, K. G., *Nature (Lond.)*, 1956, 178, 748.

Translumbar Aortography

SIR,—Mr. H. Gaylis and Dr. J. W. Laws, in their account of dissection of the aorta as a complication of translumbar aortography (*Journal*, November 17, 1956, p. 1141), have shown how easily the middle coat of the aorta can be split when the injecting medium goes astray. This easy splitting is, of course, the explanation of the dissection of the aorta in dissecting aneurysm. In 1951 I called attention to the ease with which this can be done by plucking at the inner wall of the aorta with catch forceps.[1] The cleavage is a natural one, as the separation can be readily produced in the aorta of the newly born. What still requires explanation in dissecting aneurysm is the rupture, usually transverse, into the lumen of the vessel which enables the blood to enter and cause the dissection. From the usual situation and size of these tears it seems probable that the rupture is due to physical stress. My colleague, Mr. R. Culver, a senior lecturer in civil engineering now in England on study leave, is interesting himself in the solution of this problem and I am sure would welcome any help or suggestions from our profession.—I am, etc.,

Adelaide, Australia. J. B. CLELAND.

REFERENCE

[1] Cleland, J. B., *Med. J. Aust.*, 1951, 2, 399.

Toxic Psychosis Caused by "Preludin"

SIR,—Dr. M. F. Bethell (*Journal*, January 5, p. 30) describes a patient who became irritable and suspicious and developed paranoid delusions after taking large amounts of "preludin" for some weeks prior to admission to hospital. The following notes relate to a patient who also showed marked addiction to this substance.

A married woman, aged 31 years, was brought to St. Francis Hospital mental observation ward on October 31, 1956, on an order of a duly authorized officer from a hostel where she had been staying. She had become increasingly restless, agitated, and depressed, and kept craving preludin tablets, to which she had become addicted. She stated that she had started taking them in January, 1956, for slimming, but found that besides decreasing her appetite they gave her increased self-confidence. She had increased the dosage steadily, and for the month prior to admission had been taking 60 tablets a day. However, for about six weeks prior to admission her confidence had waned; she had been sleeping poorly and become increasingly agitated and restless.

Physical examination revealed a generalized erythematous rash (which the patient stated had been present for about three months) and cutaneous hyperaesthesia of the skin of her lower limbs. Mentally she was agitated and restless, apprehensive and depressed, but had no defects in memory and no evidence of delusions or hallucinations. She became rather aggressive in manner when told that she could not have any more preludin, but after 24 hours in hospital she ceased her demands for it. Her personal history revealed abundant evidence of a "psychopathic personality." She had come from a very disturbed home background, and she had formed no close relationships with either her parents or siblings. She had never worked but drifted around forming transient relationships, and her marriage had broken up and her children been taken from her care. She had been treated at several hospitals for alcoholism and generally had proved a failure in everything she attempted (she described rather interesting parties in Soho and Chelsea, where the guests regaled themselves from bowls of "benzedrine" and "dexedrine" tablets). During the week she was in hospital she gradually settled down and became calmer, possibly aided by chlorpromazine 100 mg. three times a day. She refused to accept a mental hospital vacancy we had arranged for her as a voluntary patient and left hospital on November 8. However, after leaving hospital she recommenced preludin and was admitted to another hospital. Haematological examination revealed no abnormalities (this was done for fear of a blood dyscrasia resulting from prolonged abuse of a new drug).

There seems little doubt that in patients with a "psychopathic personality" any drug, no matter how innocuous its makers claim it to be in the normal dosage, is likely to be taken in dosages never imagined by its sponsors. Whether this justifies the placing of all such preparations in Schedule I is a matter for discussion. For example, aspirin with its known toxic and lethal effects is still freely available, despite the numerous suicides from over-dosage with it.—I am, etc.,

London, S.E.5. LEWIS CLEIN.

Glycyrrhetinic Acid

SIR,—Forgive my intrusion into a correspondence in which originally I had no intention of taking part. Since the "halloo" was sounded by Drs. R. P. Warin and C. D. Evans (*Journal*, August 25, 1956, p. 480), Dr. F. R. Bettley (*Journal*, October 13, p. 882), and Dr. B. Russell (*Journal*, November 10, p. 1113) there has been an almost unseemly rush to be in at the death of a new drug. There must be some explanation why such widely varying results with glycyrrhetinic acid have been reported.

At this stage I think it is wise to consider a few general observations which may occasionally be overlooked in the evaluation of any particular form of local treatment. Take, for example, the use of ichthyol calamine liniment in the treatment of dermatitis: (1) It may give continued relief. (2) It may relieve to begin with, but later irritate. (3) It may fail at first, but help later. (4) It may be helpful in some areas—e.g., face, neck, and arms—but only partially help or fail to help on the legs. Variations in response, provided the same batch of liniment has been used, must be due to fluctuation in the primary cause, the degree of reaction at times being greater than the degree of response. This explains the necessity at times for internal measures as well as local treatment.

Some adverse comment has been made with regard to the so-called hydrocortisone-like action of glycyrrhetinic acid. I am sure that it will be agreed that among the important effects of hydrocortisone are to be found the following: (1) an anti-pruritic effect—seen in its most dramatic form in some cases of ano-genital pruritus; (2) inflammation-masking effect—best illustrated in some cases of dermatitis of various types; (3) immunity-lowering action—seen in onset of acute impetigo after infantile eczema and a folliculitis after an irritant dermatitis. Each of these happenings has been noted, not possibly so dramatic, with the use of glycyrrhetinic acid in the following series of cases.

Treatment was carried out by members of my staff at the Western Infirmary, the Royal Hospital for Sick Children, and the Southern General Hospital in Glasgow, and to these are added a few cases seen in private practice. In some, no control was exercised other than various, and at times numerous, preceding older forms of local therapy. Others were more fully controlled. In suitable cases glycyrrhetinic acid ointment, its base, hydrocortisone ointment, and some other older applications were

applied by the ward sister, the clinical observers being unaware of the disposition of the remedies. Response noted did not necessarily mean cure.

In all, 33 patients have been treated: 8 of these were scarcely expected to improve—5 being chronic psoriasis rubra, 1 reticulosis, and 1 tinea pedis, in both of which the ointment was used to see if itch might be relieved, and finally a case of folliculitis—to see frankly whether the condition might be aggravated, as indeed happened. The remaining 25 cases were made up of dermatitis in all its forms: infantile eczema, flexural eczema, seborrhoeic, infective, sensitization, contact, exfoliative and herpetiformis (in the last-named, itch was relieved when other local measures failed), and finally 2 cases of drug eruption. Of the 25, 16 showed improvement, a specific response, 2 a non-specific response (did as well with base), 4 showed no response, and 3 were actually irritated. Of the 18 improved, 7 later relapsed, including the 2 which had shown non-specific improvement.

These results do not suggest that glycyrrhetinic acid is a panacea for all ills or even God's gift to dermatology, but they do suggest that any inference or statement that glycyrrhetinic acid is an inactive substance is both misleading and wrong. More research is necessary. It may be that a new "isomer" or a salt may be found to be more stable or active and that additional bases or an increase in percentage strength may be required.—I am, etc.,

Glasgow, C.2. JAMES SOMMERVILLE.

Herpes Zoster and Chicken-pox

SIR,—The article by Dr. R. M. McGregor on herpes zoster, chicken-pox, and cancer in general practice (*Journal*, January 12, p. 84) prompts me to record two case histories of "chicken-pox" developing after exposure to herpes zoster infection.

In the first, I myself developed, some three weeks after examining a typical case of herpes zoster, a generalized eruption resembling chicken-pox. Two weeks later my daughter, then aged 2, produced a similar eruption. Neither of us had had any relevant exposure to chicken-pox, and I had contracted it as a child. In the second, a child of 3 developed "chicken-pox" three weeks after exposure to herpes zoster. In this instance the mother, assisting a neighbour with herpes, was accustomed to take her two children with her and they would play on his bed. I have to-day examined the second child, aged 16 months, with an exactly similar rash appearing 15 days after the first. Once again there are no local chicken-pox contacts.

In my experience the rash in these cases is much less dense than in chicken-pox and the constitutional disturbance negligible. I therefore prefer to believe that it is an instance of the leopard changing his spots and that what we are observing is a form of generalized herpes zoster, analogous to generalized vaccinia, and should be properly so termed.—I am, etc.,

Hanworth, Middx. G. MELOTTE.

Drug Sensitivity Presenting as Penile Herpes

SIR,—I was interested to read Dr. John E. Underwood's letter (*Journal*, January 19, p. 162) regarding drug sensitivity presenting as a penile herpes. Phenolphthalein and sulphonamides are known to be common aetiological factors in the production of fixed drug eruptions, and the following history illustrates such a case caused by sulphadimidine.

In December, 1952, a miner, aged 26 years, developed circular erythematous patches on the dorsum of the tongue, the left side of the glans penis, the under surface of the penis, and the dorsum of the left hand, the latter showing a vesiculo-bullous eruption. The lesions were accompanied by a burning sensation and were very irritable. At first it was thought that this was a herpes, until he developed identical eruptions following the ingestion of sulphadimidine tablets in October, 1953. It transpired that the patient had a supply of the tablets which remained from the treatment of a relative's illness and which he was in the habit of taking each time he developed an upper respiratory infection. In December, 1953, when free from the latter, he was given a tablet of sulphadimidine with the subsequent production of lesions in the previously mentioned sites. Within five minutes of taking a tablet the irritation started as a burning and throbbing sensation. On the first day of the attack the lesions were red and erythematous, followed, on the second day, by multiple small vesicles which rapidly became confluent to form a bullous type of lesion. The lesions lasted for five days in all and caused the patient considerable discomfort. After the first attack there was no residual staining of the skin. The second attack, however, was followed by a very faint brownish discoloration of the skin which has remained since.

I am indebted to Dr. Peter Inman, dermatologist at the Royal Infirmary, Sunderland, for his advice on this case of fixed drug eruption.—I am, etc.,

Peterlee, Co. Durham. W. A. BROWN.

SIR,—The condition mentioned by Dr. John E. Underwood (*Journal*, January 19, p. 162) is well known to venereologists and dermatologists. It is sometimes associated with a urethritis. The syndrome has been fully described in a monograph by my friend and former colleague, Mr. A. H. Harkness.[1]—I am, etc.,

London, N.W.8. F. G. MACDONALD.

REFERENCE

[1] Harkness, A. H., *Non-gonococcal Urethritis*, 1950, p. 301. E. S. Livingstone, Edinburgh.

Neostigmine-resistant Curarization

SIR,—So-called "neostigmine-resistant curarization" cases described by Dr. A. R. Hunter (*Journal*, October 20, 1956, p. 919) have provoked many letters, but no one has been humble enough to suggest that even in these days of modern anaesthesia patients must die. As patients gradually become moribund and die all the signs seen in the neostigmine-resistant cases occur. Surely, when these elderly cases receive such an insult as an intestinal obstruction or perforation some must reach a point of no return, when they must die. I venture to suggest that this "moribund syndrome" would explain why succinylcholine, gallamine, curare, serum potassium, and other biochemical estimations are collectively or severally castigated. If Dr. Albert Christie (*Journal*, December 1, p. 1303) happened to tackle a "moribund syndrome" case with his "less spectacular method" he would view the post-operative peripheral failure, gradual intercostal and diaphragmatic paralysis, and death in proper perspective.—I am, etc.,

Adelaide, Australia. J. A. SCANLON.

Psychiatry in Africa

SIR,—In his article on neuropsychiatric problems in Nigeria (*Journal*, December 15, 1956, p. 1388) Dr. Adeoye Lambo, within a few paragraphs, makes the following statements: "Some of the native treatment centres which I have seen may well play a useful part in solving our immediate problems. Their psychotherapeutic measures are as effective and as scientifically sound as any I have seen practised in Europe." "It is known that institutionalized confessions, trances, dances, and primitive religious rites and ceremonies, all of which are found to form the basis of the treatment armamentarium of these centres, are powerful psychotherapeutic measures."

Dr. Lambo goes on to quote approvingly another authority who has emphasized "the tremendous psychotherapeutic power which magic has, not only for those for whom it is performed, but above all for the performer himself." He further states that "these native treatment centres claim greater success in the sphere of neuroses [greater than what we are not told]. Some of the medicine-men think that incipient or latent psychosis responds in the same way." I have no wish to minimize the enormous difficulties under which Dr. Lambo and his colleagues have to work in a grossly under-doctored area, but it would be derogatory to his dignity as an African trained in our medical schools to pass some of these remarkable statements without criticism.

(1) Is the claim that psychology and psychiatry are scientific disciplines valid in Western Europe, when their results are reproducible and even bettered by primitive magic in Africa? (2) Dr. Lambo endorses Tooth's[1] statement: "So that, until African psychiatrists can be trained, it would seem better to allow the care of the majority of the insane to remain in lay hands." What conceivable reason is there for training Africans in the principles of Western psychiatry if their own psychotherapeutic measures practised at the natives centres "are as effective and as scientifically sound" as any seen in Europe?

The *B.M.J.* is the official organ of the B.M.A., one of whose primary objects is the promotion of the medical and allied sciences (*B.M.A. Year Book, 1956–7*). You, Sir, have an annotation (p. 1420) on Dr. Lambo's article without once commenting on the use of magic in medical treatment, so patently commended by the author. I should be glad to know how you reconcile this omission with the declared objects of the Association.—I am, etc.,

Glasgow, W.2. A. STEWART HENDERSON.

REFERENCE

[1] Tooth, G., *Studies in Mental Illness in the Gold Coast*, 1950. Colonial Res. Publ. No. 6. H.M.S.O., London.

Common Infectious Diseases in General Practice

SIR,—Dr. G. I. Watson's excellent article on common infectious diseases in general practice (*Journal*, January 5, p. 39) is indeed thought-provoking. I would take issue with him on one point particularly, and that is his "German measles tea parties" for schoolgirls. It is believed that permanent immunity almost always results from a single attack of rubella. But how effective is this "tea-party" immunity and what degree of protection will still exist after perhaps 10 or 20 years? Secondly, there is an obvious risk that some of the "tea-party" girls might have mothers in the early stages of pregnancy. Also, what about the girls that would contract a mild infection or show no symptoms or signs at all? Could it be assumed that this was due to inherent immunity, or should they be exposed to a further attack and, if so, when? Lastly, German measles is usually a minor ailment, but the possibility of severe infection and even neurological complications cannot be ruled out. Much more experience is required before such an unusual procedure can be recommended.[1]—I am, etc.,

Taunton. J. G. P. POWER.

REFERENCE

[1] *Memorandum on the Closure of Schools and Exclusion from School on Account of Infectious Illness*, 1956. Jointly issued by Ministry of Education and Ministry of Health. H.M. Stationery Office, London.

Tonsils and Adenoids

SIR,—I read with interest Dr. John Fry's article, "Are All 'T's and A's' Really Necessary?" (*Journal*, January 19, p. 124). That he is not the first to ask this question enhances rather than reduces the value of his observations. While I am in substantial agreement with these, may I be allowed to make a few comments?

(1) He does not distinguish clearly between the indications for tonsillectomy and adenoidectomy. Although, for practical reasons, the two operations are often performed at the same time, it is important to realize that the indications are distinct and that it may be correct to perform one only. I have in mind particularly adenoidectomy without tonsillectomy. (2) In adults tonsillectomy is rarely criticized because, when done for good reasons, the result is only beneficial. It is probable that the pathology of "chronic tonsillitis" in adults and children is not quite the same, but perhaps sauce for the goose is sometimes sauce for the gosling. (3) There seems little doubt that the tonsils have a definite function in early childhood, as the late A. J. Wright suggested in his Semon Lecture in 1949.[1] The removal of tonsils which are still functioning may result in compensatory hyperplasia of the other lymphoid structures of the pharynx. As this may cause a chronic sore throat which is almost untreatable, we must certainly be chary of operating on young children unless the reasons are very good. In my experience this does not apply to adenoidectomy.

We should ask ourselves, "Is it really necessary?" before advising any operation, and this is particularly so with tonsillectomy.—I am, etc.,

Taunton PETER HUGGILL.

REFERENCE

[1] Wright, A. J., *J. Laryng.*, 1950, **64**, 1.

SIR,—Unfortunately, provocative articles in medical journals are eagerly seized on by the popular press, as in the case of Dr. John Fry's paper (*Journal*, January 19, p. 124). As a result, an operation which Dr. Fry admits to be useful and valuable in its place tends to be discredited in the public mind. Surely the fact that the number of tonsillectomies per 100 children has fallen by half in the past twenty years is evidence that the more critical approach sought by Dr. Fry already exists.

A list has been given of "the most usual reasons" for operation, which ought not to be confused with the indications, although Dr. Fry has combined them. Among the proper indications are several not mentioned—after peritonsillitis, which does occur in childhood (tonsillectomy), chronic otitis media maintained by nasopharyngeal infection, persisting conductive deafness, and chronic suppurative sinusitis (adenoidectomy). Borderline cases are decided between the G.P. and the E.N.T. surgeon: the latter is no more "in a quandary" than is any surgeon when asked to see any patient referred from a practitioner for consideration of an operation. Lastly, many adult tonsillectomies are still required in spite of the high rate of incidence of operation in children in the past.—I am, etc.,

Maidstone. J. D. TRETHOWAN.

SIR,—Dr. John Fry's interesting and stimulating paper on tonsillectomy (*Journal*, January 19, p. 124) would have been of greater scientific value if it had been possible to include two control series from other practices. Dr. Fry's statistics suggest that the harmful effect sometimes produced by enlarged tonsils and adenoids often disappears, but takes some years to do so. It would be of interest to know whether this period is significantly cut short (1) where tonsillectomy is done as a routine, and (2) where cases are selected but the net is spread much wider than in Dr. Fry's practice. Three points would be worth considering in particular: the amount of medical attention required for, say, three years after operation; the rate of growth; and absenteeism from school. If these are significantly affected, surely most doctors and parents would agree that operation was worth while at a time of life when satisfactory development is so important.

My first eight years in practice were in an industrial area, where definite indications for removal of tonsils and adenoids seemed very frequent. It was usual for the children to grow more rapidly, and not to need attention for ailments of any kind, for two or three years after operation. With rare exceptions the operation was done at home, in any kind of home. Possibly that is why psychological trauma did not occur. One boy, seeing the benefit to his elder brother, asked to have his own tonsils removed. Complications were very rare. There were no sulphonamides then, but also no cross-infections in the patient's own home.—I am, etc.,

Bracknell, Berks L. G. JACOB.

SIR,—Dr. John Fry's stimulating and provoking article (*Journal*, January 19, p. 124) shows a capacity for statistical research. He neglects, however, the most important factors. "A prophylactic ritual carried out for no particular reason with no particular result." This misstatement by the M.R.C.[1] offers the answer. There is a reason. There is a result. The sacrifice of lymphoid tissue pacifies the parents and relieves the general practitioner of anxiety and frustration.

What is the family doctor expected to treat? A natural hypertrophy? A sore throat without pathogens? A running nose in a child that neither sniffs nor blows? Mechanical

irritative and obstructive features of the upper respiratory tract? Not surprisingly, the results are bad. Why does the family doctor treat the child? Mother's complaint that the child is always ill is belied by its appearance. Her continuous anxiety, despair, guilt, and agitation are transferred to the practitioner, and "Something must be done" leads to the mutilation. It must not be assumed that all cases of recurrent catarrh and sore throats are brought to the doctor. Witness the children running to school coughing, spluttering, and noses dripping, but still laughing and happy. Surprisingly, no comment has been offered on the child's own reaction to his illness: the warmth and comfort of bed, the attempt at spoiling, the singling out from the siblings for extra favours, and the holding up to ransom of the parents. Even where the inner need for retributive punishment is causative, where the child hates the enforced rest, these factors may easily be elucidated.

The mother's overt anxiety is accepted as a direct result of the child's condition. Her related deeper anxieties, unconscious like her guilt, remain unrecognized and indeed neglected. Irrespective of her aggression to the child or her over-indulgence of it, these are the factors at play. The mother desires cure of her own illness and offers a sacrifice. The result of operation relieves mother's anxiety temporarily, and the assessment of improvement is of her own condition. The child's growing-up problems, his jealousies, fears, and difficulties of adjustment—in these spheres lies the answer to the catarrhal child. The problem is one of utilization of illness by the parents and, less commonly, the child, sickness that is rarely infective or allergic but is almost always psychogenic.

Dr. Fry describes anxiety in the child's parents, relatives, and teacher, but offers them a policy of *laissez faire* and sympathy. He prefers to wait for the child to grow out of his catarrhal stage to save enormous operation costs, but this will not affect the mental health of the mother, nor make her a less frequent visitor to his surgery. A direct psychotherapeutic approach and the elucidation of the meaning of the illness to the mother is required. He finds anxiety and agitation in everyone but the child, and offers sympathy instead of psychotherapy. Over the past two years I have seen no child deserving tonsillectomy but many mothers requiring psychotherapy. Correlation of the pre-Oedipal and Oedipus phases with the normally accepted illnesses of childhood has yet to be finally assessed. In the hands of the general practitioner lies the opportunity for increasing efficient psychotherapy and less referral to otorhinology. —I am, etc.,

Sidcup. L. A. NICHOLS.

REFERENCE

[1] Medical Research Council, *Spec. Rep. Ser.*, 1938, No. 227.

Sudden Infant Deaths

SIR,—The paper on sudden unexpected death in infants by Dr. J. L. Emery and Miss E. M. Crowley (*Journal*, December 29, 1956, p. 1518) does not in our view help to elucidate this difficult problem, and may in fact give false impressions. While we agree that the case history taken by the coroner's officer may be at variance with that taken subsequently by one trained in a different manner, it is doubtful if either version can contribute materially to providing a more accurate diagnosis in obscure cases. Many infants, especially at this time of year, have either mild respiratory or gastro-intestinal symptoms, and it would be of some interest had the authors interviewed 50 control mothers whose babies did not die. Following the tragedy of an unexplained death it is the natural tendency of both parents to remember and magnify a minor ailment, which may or may not be of importance. The group showing no significant symptoms remains.

Do the authors really believe that, had some attention been paid to the symptoms, many of the cases could have been diagnosed and treated? We have carried out necropsies when the symptoms prior to death were absent or minimal, and no satisfactory cause could be discovered either histologically or bacteriologically. They represent about a third of the cases of sudden death in infants, and we think that such a view would be unfair to both the parents and the family doctor. The authors' statement that their policy is "to give some definite cause of death at inquests" puzzles us. What causes do they give in such cases? Do the authors feel that it is safe to put a baby in a cot with a pillow, especially when it is ailing? We fear that it will be necessary to suspend judgment in this important matter until new methods of examination for virus infections become available to the routine pathologist. —We are, etc.,

Southampton. E. S. DUTHIE. R. A. GOODBODY.

Bolus Obstruction

SIR,—I feel that brief mention of the following two cases may be of interest, particularly at this time of year. During the course of one afternoon two men were admitted to the Merthyr General Hospital from widely separated areas. Both gave a history of severe upper abdominal pain and vomiting for six hours. The possibility of an acute pancreatitis or perforated peptic ulcer was considered and a laparotomy was performed in each case. Both were found to have a brussels sprout impacted in the ileum, in one case 1 ft. (30 cm.) and in the other case 2 ft. (61 cm.) from the ileocaecal valve. The obstruction was relieved by removing the bolus, and recovery ensued. I do not recollect seeing mention of brussels sprouts among the numerous food materials cited as causes of bolus obstruction, and these cases illustrate their potential danger if not properly masticated. Once again, it may be said that food which enters as a friend may become an enemy in our midst.—I am, etc.,

Merthyr Tydfil. R. J. WILLIAMS.

Advertisements for Cigarettes

SIR,—The leading article on mortality and smoking (*Journal*, November 10, 1956, p. 1104) ended with these impressive words: "The new evidence now published makes it more than ever imperative for all concerned to see that the public is repeatedly informed of the possible dangers to health and life from smoking cigarettes." But the same issue of the *Journal* carried a full-page advertisement for one brand of cigarettes. My inquiry about this striking inconsistency was referred to the Journal Committee, which has since resolved that no action should be taken. Its policy remains "to take advertisements for cigarettes, provided the 'copy' is acceptable."

To continue advertising cigarettes in the face of the overwhelming medical evidence of the dangers of tobacco addiction can only be considered extremely reprehensible, more especially when we recall that the most damning indictment is based upon the high death rates among heavy-smoking doctors (Dr. R. Doll and Professor A. Bradford Hill, p. 1071). The *Journal of the American Medical Association* refuses to carry tobacco advertisements. This enlightened attitude was urgently adopted in 1954—when the mortality rate from bronchogenic carcinoma in the United States was only half that in England. What possible excuse can the *British Medical Journal* offer for not following this example? In protest against the *Journal's* refusal to practise what it preaches, I am tendering my resignation from the B.M.A.—I am, etc.,

Leicester. J. P. ANDERSON.

Carcinoma of Cervix and Corpus Uteri

SIR,—It is commonly held that carcinoma of the cervix uteri is much more common than carcinoma of the corpus —e.g., Anderson,[1] "Carcinoma of the cervix composes about 90% of all uterine cancer"; Novak,[2] "In round figures it may be said that about 1 out of every 8 uterine cancers will be found to be of the body type"; and Willis,[3] "Broadly it may be said that cervical carcinoma is three or four times

as common as endometrial." Probably the proportion given by Willis is that found in the large industrial centres of Great Britain, but this may be untrue in rural areas. In this rural area carcinoma of the cervix has formed only about one-third of the total cases of uterine carcinoma during the past few years, and Dr. E. M. Martland tells me that for many years before this it has formed only a small proportion. This low proportion is not due to patients with cervical carcinoma by-passing the hospital here by being sent direct to a radiotherapy centre, and biopsies are taken here irrespective of whether further treatment is to be surgical or by irradiation.

The table shows the figures from (1) a large industrial centre, (2) two mainly rural areas, and (3) from three rural areas.

Centre	Period (Months)	Carc. Cervix	Carc. Body	C/B
Jessop Hosp., Sheffield ..	24	127	44	2·91
Carlisle	39	102	78	1·31
Winchester	60	65	50	1·30
Portsmouth	36	111	89	1·20
Bournemouth	24	31	34	0·94
Salisbury	24	16	30	0·53

It would be unwise at the moment to speculate on possible reasons for a difference in incidence between industrial and rural populations. Far more figures than those given above are necessary to establish that there is in fact such a difference. I should be grateful to receive figures from pathologists throughout the country, and meanwhile I thank Drs. C. G. Paine, J. S. Faulds, H. G. H. Richards, J. D. Clay, and T. K. Owen for the figures quoted above.—I am, etc.,

General Infirmary, Salisbury, Wilts. H. E. HARDING.

REFERENCES

1 Anderson, W. A. D., *Pathology*, 1948. St. Louis.
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Congenital Absence of Spleen

SIR,—Your annotation (*Journal*, January 19, p. 153) states that congenital absence of the spleen is a rare anomaly. In a series of 126 cases of congenital abnormalities of the heart and great vessels coming to necropsy, mostly in the first year of life, I have encountered three cases in which the spleen was absent; two showed dextrocardia associated with Fallot's tetralogy and ostium atrioventriculare commune respectively, while the third showed transposition of the great vessels; in none was situs inversus of any abdominal viscera present.

The assessment of the rarity of a condition rests largely upon the frequency with which it appears in the literature. Congenital anomalies of the heart of sufficient severity to cause death within the first few weeks of life are generally not considered of sufficient interest to warrant publication, but it is in this group that absence of the spleen is most common. Since the anomaly probably arises in the fifth to seventh week of intrauterine life it would be surprising if it were not a relatively frequent incidental finding in any series of infantile deaths due to severe cardiac anomalies.—I am, etc.,

London, E.2. N. E. FRANCE.

Pregnancy Sickness

SIR,—Recent letters from Dr. Doreen S. Ball (*Journal*, December 22, 1956, p. 1487) and Dr. R. Bauer and Dr. Margaret MacFetridge (*Journal*, January 12, p. 105) provide further evidence of the complete failure of research into the aetiology of pregnancy sickness. Further evidence, if any is needed, is provided by the multiplicity of drugs, diets, and routines recommended by the different adherents, and, incidentally, all of them equally useless. Dr. Bauer suggests an allergic basis for some of the cases, and on that ground explains the effectiveness of antihistamines in some. On the other hand, is it not possible that the success of antihistamines might be due to (1) suggestion, (2) sedative action, and/or (3) an action similar to that in travel sickness? Dr. MacFetridge feels that it is possible that the trouble may be due to hormonal imbalance, and describes the sickness and nausea caused by stilboestrol (taken to stop lactation) as identical to the nausea and vomiting of pregnancy. Here again there seems to be an anomaly, because large doses of stilboestrol seem to be very well tolerated when given to terminate lactation. Similarly, large doses are well tolerated indefinitely when given to men with carcinoma of the prostate.

Finally, there are a number of cases of pregnancy sickness which never reach either the antenatal clinics or the obstetricians. I refer to sickness in "expectant fathers." Reference to the literature reveals little mention of this type of sickness. F. J. Browne[1] mentions one case reported by Atlee in support of his psychological theory. I am sure, however, that this type of sickness is much more common than is generally appreciated. Over the past year I can call to mind four cases of men who suffered from typical pregnancy sickness. In each case the sickness of the wife was much less than with previous pregnancies. In one case pregnancy was not even suspected (so I am assured) and sickness was absent in the wife but typical in the husband. In another case sickness was controlled in both husband and wife by a widely advertised pregnancy sickness tablet. It would seem that here is a condition which could be the subject of large-scale research by general practitioners under the supervision of the College of General Practitioners.—I am, etc.,

Nuneaton, Warwicks. K. L. H. FLYNN.

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Incidence of Diphtheria

SIR,—The fall in the incidence of diphtheria in the past few years is much more striking than is shown in your table (*Journal*, January 19, p. 176), which is evidently based on uncorrected notifications. The figures for corrected notifications, as published by the Registrar-General, are approximately one-quarter of those in your table. During 1954 and 1955 the total corrected numbers of cases for the whole year were approximately one-fifth of the average weekly numbers in the pre-immunization period.—I am, etc.,

London, W.C.2. H. I. WINNER.

Rupture of Hind-waters and Haemorrhage

SIR,—I have read the report by Dr. J. K. Russell, Mr. D. F. Smith, and Mr. R. Yule (*Journal*, December 15, 1956, p. 1414) with interest. In their discussion they mention their practice of sweeping the membranes off the lower uterine segment as far as it can be reached with the examining finger before puncturing the hind-waters with the Drew Smythe catheter, but point out that the placenta may not be reached.

With this instrument the amniotomy is performed through an area which cannot be assessed by palpation; bleeding is a frequent occurrence as a result of passing the catheter between the placenta and the uterine wall, and should be an indication for its withdrawal and passage in a direction at least 90° from the original. With low puncture of the membranes and drainage of the fore-waters the amniotomy is performed through a part of the membranes which has been palpated and may even have been visualized, hence disruption of the placenta from its site is obviated. Only once out of many hundreds of cases have I seen foetal bleeding occur, from an unsuspected vasa praevia, in a case of induction by low puncture of the membranes.

In the two cases reported the causes of death are given as being due to or contributed to by the exsanguination, yet the haemoglobin in the child delivered alive was estimated

at 10.3 g. per 100 ml. and the amount of blood lost 90 ml. In the other infant the loss was heavier. However, both these were the offspring of mothers suffering from toxaemia of pregnancy, and in one case (the stillbirth) labour occurred nine days after her expected date of delivery. The post-mortem findings in case 1 are consistent with the baby having died from toxaemia, possibly aggravated by the blood transfusion, but the abrupt cessation of the carefully recorded foetal heart in the early stages of labour at or about 10 days over term is common. It would thus seem that, though blood loss from the foetal circulation is to be avoided, neither of these deaths can truly be laid to this cause.

In these two case reports, and according to their "invariable" practice of sweeping the membranes off the lower uterine segment, it would appear that the os admitted the examining finger with ease, and I suggest that, given such conditions, low puncture of the membranes is a safer procedure for the foetus and a more certain method of inducing labour without the time-lag of 24–36 hours usual with draining the hind-waters. The examining finger in such cases is also able to exclude the presence of a cord presenting with danger of prolapse at the time of "bursting of the waters," whether spontaneous or artificial.

As a method of induction of labour the Drew Smythe catheter has another disadvantage, shown by Dr. Russell and his colleagues, to add to the uncertainty of the method, the slow response where successful, the danger of placental separation (especially in toxaemia where repeated small infarcts may have brought the placental sufficiency to a borderline level), and the danger of intra-amniotic infection by contamination.—I am, etc.,

Nova Scotia. HENRY FITZGIBBON.

Vaginitis

SIR,—We were very interested in your annotation entitled "Vaginitis" (*Journal*, January 19, p. 155), for in this clinic we treat a considerable number of cases of vaginitis due to *Trichomonas vaginalis* and to *Candida albicans*. We are surprised, however, that you recommend the use of "an oral trichomonicide such as aminitrazole." Our own experience with trichomonicides, including aminitrazole, has been most discouraging. Administration of aminitrazole alone, unsupported by local treatment, has, as far as we have been able to observe, no therapeutic effect whatsoever. It therefore seems to us unlikely that this drug contributes in any way to the efficacy of the scheme of treatment described. We should be interested to know details of the experience of others with oral trichomonicides.—We are, etc.,

R. D. CATTERALL.
E. M. C. DUNLOP.
EVA GALLAGHER.

London, E.1.

Varicose Ulcers

SIR,—The logical and successful treatment of any disease depends upon the knowledge and application of certain fundamental principles. This applies no less to the healing and prevention of varicose ulcers. The number of diverse treatments for varicose ulcer is mainly due to lack of understanding or failure to apply these principles.

First, it is necessary to understand the process of repair. A surgical wound, even though strictly aseptic, is not bacteriologically sterile. Carrel[1] demonstrated that an aseptic wound will not heal if all debris and blood clots are removed and the wound is protected from outside irritation. An open wound heals from below by granulation, and the youngest tissue is at the surface; it is highly vascular and bleeds readily. Healing is delayed if these granulations are torn off or caused to bleed. The use of antibiotics in treating a varicose ulcer is unnecessary and may retard healing. It does not matter what sort of dressing is used on the ulcer, provided the patient is not sensitive to it and provided it does not stick to or in any way damage the granulations.

Secondly, it is necessary to understand and apply the teaching of Hilton.[2] A varicose ulcer can be completely at rest when the patient is walking about and is not necessarily at rest when the patient is in bed. To immobilize a varicose ulcer the leg should be bandaged from the toes to the tibial tubercle, and the heel must be included. It does not matter what sort of bandage or support is used, so long as there is a firm, even pressure to the skin. If the bandaging is efficient it will control the high-pressure venous leaks in the deep fascia in the same way that a truss controls a hernia. The so-called calf pump is repaired, and when the patient walks the blood supply to the ulcer is improved, and also the oedema rapidly disappears. Activity is therefore an essential part of the treatment.

By applying these principles I have been able to heal every varicose ulcer I have treated, except one which was owned by a lady who persistently removed her bandages. I include patients whose work involves standing all day and who continue to work during treatment, and one patient with an artificial limb. Zinc oxide spread on gauze is a convenient and cheap dressing which does not stick. Two 4-in. (10-cm.) crêpe bandages are far more comfortable for the patient than "elastoplast" or elastic webbing and are much easier to apply. Patients with ulcers less than 2 in. (5 cm.) in diameter I treat in the normal course of the surgery and can dress and bandage them in less than five minutes. In conclusion, there is no more grateful patient than one whose varicose ulcer has been healed without time off from work, particularly if he has previously had operative treatment. In order that he shall remain grateful it is necessary to explain that his ulcer will recur unless he continues to wear support for most of the time and to advise him to raise the foot of his bed about 3 in. (7.5 cm.).—I am, etc.,

Staines, Middx. PETER DARBY.

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2 Hilton, J., *Rest and Pain*, 1863. London.

Antibiotic Cover for Dental Extractions

SIR,—We have read the letters from Dr. R. Cutler and Mr. Adrian Cowan (*Journal*, January 19, p. 162). It was our sincere hope that our communication (*Journal*, December 29, 1956, p. 1501) would revive interest in the fundamental observations of Okell and Elliott[1] and later of Elliott,[2] that a *Str. viridans* bacteriaemia follows not only the major trauma of dental extractions but also the rocking of teeth in infected gum sockets in the course of mastication and teeth grinding.

The mouth, gums, and dental sockets are the normal habitat of *Str. viridans*, and it is improbable that by any local or systemic medication the organism will be eliminated even for short periods of time. It is our belief that so long as teeth or dental remnants are present in the jaws the ideal mechanism is present to produce a *Str. viridans* bacteriaemia. For any patient who has developed subacute bacterial endocarditis due to *Str. viridans* we believe that this dangerous mechanism should be completely eliminated. In the cases referred to in our communication the opinions upon the teeth of our patients were those expressed by the clinical dental staff of the hospital and the radiologists whose opinion was sought in specific relation to the possibility of any evident and treatable source of infection in the teeth or gums. "Good" indicated that no defect was detected by either dentist or radiologist; "bad" indicated that defects were present. Whatever steps are taken to promote the more rapid healing of a dental socket *after* the extraction of a tooth, these are unlikely to control the bacteriaemia incidental to the extraction.—We are, etc.,

F. G. HOBSON.
B. JUEL-JENSEN.

Oxford.

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2 Elliott, S. D., *Proc. roy. Soc. Med.*, 1939, **32**, 747.

Obituary

C. L. GIMBLETT, M.D., F.R.C.S., M.R.C.P.

Mr. C. L. Gimblett, formerly senior surgeon at the Westminster Branch of Moorfields Eye Hospital, died in the Westminster Hospital on January 21, aged 66.

Charles Leonard Gimblett was born on June 19, 1890, the only son of Robert Wheddon Gimblett, of Somerset. From Clifton College he went on to Gonville and Caius College, Cambridge, where he took the Natural Sciences Tripos, continuing his clinical studies at St. Thomas's Hospital. Qualifying in 1914, he graduated M.B., B.Ch. the following year, proceeded to the M.D. in 1918, and took the M.R.C.P. in 1919 and the F.R.C.S. in 1922. At St. Thomas's he was casualty officer, house-surgeon, house-physician, resident anaesthetist, and senior ophthalmic house-surgeon, but before completing this impressive series of house appointments he served from 1915 to 1919 in the Royal Navy, like so many of his name. Early in his career he decided to devote himself to ophthalmology, and during part of his wartime service he was in charge of the eye departments at the Royal Naval hospitals at Portland and Chatham. In 1923 he was appointed assistant surgeon to the Royal Westminster Ophthalmic Hospital and ophthalmic surgeon to the Royal Northern Hospital, and he was also ophthalmic surgeon to the East Ham Education Committee, for which he prepared a report on the incidence of myopia in the schoolchildren in the borough during the years 1920 to 1926. In 1927 he became full surgeon at the Royal Westminster Ophthalmic Hospital, and twenty years later senior surgeon there, retiring from the active staff last August. During the second world war he worked at the Haymeads Hospital, Bishop's Stortford, and was appointed to the staff of the General Hospital in that town. For nearly twenty years he was a member of the staff of the Lord Mayor Treloar Orthopaedic Hospital at Alton, a hospital for which he always had a very great love. Last July he was appointed emeritus consultant there, and he remained chairman of the medical advisory committee up till the time of his death.

Orthoptics was Mr. Gimblett's special interest, but he wrote on a variety of subjects and contributed the chapter on eye diseases in Romanis and Mitchiner's *Science and Practice of Surgery*. In 1949 he was elected vice-president of the Ophthalmic Section at the Royal Society of Medicine.

Mr. Gimblett married Audreen Isobel McKenzie McNicol in 1935, and she survives him with two sons.

G. G. P. writes: Mr. Gimblett was keenly interested in orthoptics, carrying on the work of Claud Worth, whose practice he took over, and on the inception of the orthoptic department at the Royal Westminster Ophthalmic Hospital he was appointed medical officer in charge. He was also the first chairman of the Orthoptic Board. A clinical ophthalmologist of the best kind, he never spared himself and was always painstakingly thorough in his work. It was with the utmost difficulty that he could be persuaded to take a holiday. In spite of two severe illnesses he continued his hospital work, even going on after the normal retiring age when asked to do so. He continued with his private practice right to the end. He was beloved by his patients, with whom he was patient and tactful to a degree, and by his colleagues, to whom he was a loyal and faithful friend and who always enjoyed his charming sense of humour. His services were invaluable as chairman of the medical committee and on other committees at the Westminster Branch of Moorfields. He had a fine collection of books on mediaeval art. His delight when he did take a holiday was to go to the Mull of Kintyre with his family and have a sailing holiday. All his many friends will extend their deepest sympathy to Mrs. Gimblett and her sons in their grievous loss.

J. D. BENJAFIELD, M.D., D.P.H.

Dr. J. D. Benjafield, formerly bacteriologist at St. George's Hospital, died in his sleep at his home in London on January 21. He was 69 years of age.

Joseph Dudley Benjafield was born in London on August 6, 1887, the son of Dr. W. B. Benjafield, and was educated at Marlborough College and at University College Hospital, London. He qualified by taking the London Conjoint diploma in 1909, and in the following year he obtained the London University degrees of M.B., B.S., with honours in medicine. He proceeded to the M.D. in 1912, and in 1924 took the D.P.H. of the English Royal Colleges. After qualification he held the appointments of house-surgeon at the Evelina Hospital for Sick Children and house-physician at University College Hospital. From 1913 to 1920 he was bacteriologist to the Western Skin Hospital, in the Hampstead Road, and the Kensington, Fulham, and Chelsea General Hospital, and, later, to the All Saints' Hospital for Genito-urinary Diseases. He served in the R.A.M.C. from 1915 to 1919 during the first world war and from 1940 to 1942 in the second world war. After demobilization in 1919 he was appointed assistant bacteriologist at St. George's Hospital and lecturer in bacteriology in the medical school, where subsequently he became lecturer in clinical pathology.

In his younger days Benjafield was a well-known racing driver of Bentleys at Brooklands and Le Mans, where, with Mr. S. C. H. Davis, he won the Grand Prix d'Endurance in 1927. Two years later he came in fourth. A founder member of the British Racing Drivers' Club, he was a vice-president and former treasurer. His enthusiasm was infectious and did much to encourage British drivers to enter for the Le Mans events and similar meetings on the Continent. He leaves a widow and a son.

J. A. B. writes: Benjafield was not a learned bacteriologist. He was, in fact, a clinical pathologist whose theory and practice were derived from the time early in this century when it was hoped that the lessons of bacteriology might be applied usefully not only to the diagnosis but to the treatment of the individual patient. The fashion waned (until revived by antibiotic treatment), but Dudley remained faithful to the meticulous examination of cultures from every orifice of the body and to treatment with vaccines from these sources. The theory may have been unsound and its application outmoded, but he remained a successful and much-loved consultant because each one of his patients, in hospital and in Harley Street, was to him an individual with whose troubles he sympathized and for whom he did his very best. When he went on holiday he used to leave me a catalogue of notes on expected patients, which were masterly summaries not only of their ailments but of their virtues and failings.

Although he put on weight quite early in life his energy was amazing. He performed his teaching and other duties at St. George's scrupulously. He held appointments at other hospitals, and his private practice was very large. He always arrived in a hurry (and in later years rather out of breath), but time was never too short for his cheerful courtesy to great and small. He played as hard as he worked. Others can tell of his motor racing; I found a journey in his car

unrestful. When he abandoned this sport for fishing he became a skilful if rather petulant angler, but there were no bounds to his enthusiasm. A few hours after salmon in the Teifi were to him well worth a drive to West Wales and back crammed into a short week-end. He appreciated personal and material elegance, and he liked the pleasures of the table. Above all, he liked the life he led, and retirement had no attraction for him. He had few illusions about his fellow men and none about himself. Many of us must be grateful for having enjoyed his friendship.

Dr. REX BINNING writes: I first met Dudley Benjafield when I was a student at St. George's Hospital. He was a popular figure among the students, for his prowess as a racing motorist was well known. He was a most patient lecturer and demonstrator of bacteriology and an excellent teacher of laboratory technique. In addition to being a first-class bacteriologist he was also a very wise and shrewd clinician. As students, we learned to respect his ready wit and biting tongue, but it never left a mark except upon the pompous or petty-minded. Dudley Benjafield was always young in mind, and had many friends among his juniors. His counsel was often sought, but never in vain. In 1941 I shared a cabin with Benjafield in a crowded troopship making the long and tedious voyage round the Cape. I then came to know him better and to admire his active mind and capacity for work. He decided to write his reminiscences of his motor-racing days, and on hot sweltering afternoons in the tropics, when most of us were lying in our bunks, he would be writing the 3,000 words that were his target for the day. At night, after perhaps an evening playing poker, he would read over to me what he had written. When I myself was confined to my bunk with a carbuncle he was kindness itself, directing the treatment, doing the dressings himself, and bringing me my meals. Dudley Benjafield will be mourned by a host of friends, who will remember him for his zest for life, for his wit, his charm, and for many acts of kindness that were known only to a few.

CHARLES NOON, O.B.E., F.R.C.S.

Mr. Charles Noon, formerly senior surgeon to the Norfolk and Norwich Hospital, died at his home at Norwich on January 19 at the age of 71.

Born in Leicester on November 22, 1885, Charles Noon was educated at Blairlodge School, Stirling, and at St. Bartholomew's Hospital Medical School. Qualifying in 1910, he held the appointments of house-surgeon and resident anaesthetist at St. Bartholomew's Hospital, house-physician at the Royal Northern Hospital, and resident chief assistant to the department of gynaecology at St. Bartholomew's Hospital. Having taken the F.R.C.S. in 1914, he went to Norwich in the following year as a major in the R.A.M.C., taking charge of the surgical section of the Thorpe War Hospital, a post which he held until the end of the war. For his services there he was appointed O.B.E. in 1919. In that year also he was elected assistant surgeon to the Norfolk and Norwich Hospital, becoming full surgeon in 1932 and senior surgeon in 1946. He retired from the active staff in 1955. He was also consultant surgeon to many local hospitals, including St. Andrew's Hospital, Thorpe, the West Norwich Hospital, and the Jenny Lind Hospital for Children. Always keenly interested in the welfare of war pensioners, Mr. Noon was at one time surgeon-in-charge of the Ministry of Pensions out-patient clinics and limb-fitting centre at Norwich. Treatment of malignant disease by radium therapy was a method which he had studied closely, and over thirty years ago he purchased his own supply of radium, which he used freely in the hospitals to which he was attached. During the second world war he was once again in charge of the Thorpe Hospital, this time under the Emergency Medical Service. Since the inception of the National Health Service he had been a member of the surgical advisory committee of the East Anglian Regional Hospital Board.

He married Cicely, daughter of Mr. F. South, and she survives him, together with one son.

J. M. R. T. writes: Charles Noon was a shrewd and far-seeing man whose advice and guidance, willingly given, were always of the utmost value. To those who met him for the first time he could give the impression of being remote and even cynical, but to the few who were privileged to know him well real kindness was the mainspring of his personality. Surgery was the absorbing interest of his life. Gifted with a profound clinical instinct, he taught generations of registrars and housemen to use their five senses rather than to rely on the "investigations" judged indispensable in the surgery to-day. His out-patient clinics, ward rounds, and operating sessions were enlivened by his forthright personality, his great store of surgical aphorisms, and his wide knowledge of medical history. He was a man who never suffered fools gladly, and he always expected everyone to give of his best.

Charles Noon was an enthusiastic bibliophile and collector, but among his many treasures his books and papers relating to every facet of the medical work and history of Bart's took pride of place. His enthusiasm and admiration for his own teaching school never waned. It was an education in itself to hear him talk when surrounded by the *lares et penates* which he had acquired with the discerning patience of a connoisseur.

P. S. FLEISCHMAN, M.D.

Dr. Paul S. Fleischman, who might be regarded as the doyen of the group of German doctors who came to Britain in the days of the Third Reich, died in the Regent's Park Nursing Home on January 16 after a short but not unexpected illness at the age of 77.

He was born on July 23, 1879, of a well-known banking family at Fürth, in Bavaria, and on his mother's side he was related to the famous Romberg. His school days were spent in Berlin, but he returned to Bavaria for his medical studies at Munich, where one of his teachers was Röntgen, and he graduated in medicine in 1902. After qualification he travelled and studied in many centres, in Paris with Metchnikoff, in London with Sir Almroth Wright, in Berne with Sahli and Kronecker, and then he went to the famous Charité in Berlin, working under von Leyden and His, father and son. Rising through the various stages of this German medical faculty, he was eventually appointed after fifteen years of junior posts as "ausserordentlicher" professor at the Charité Hospital. The two "ordinarius" professors at this time were the famous and witty Friedrich Kraus and Wilhelm His of "bundle" fame. Wilhelm His was particularly fond of Fleischman, who was his chosen doctor in his last illness, being not only his medical adviser but his intimate friend.

Other appointments followed, numerous papers from his pen appeared in the German literature in these years, and he became one of the most sought-after physicians in Berlin. Then at the height of his career came tragedy, and humiliation after humiliation was heaped upon him until finally his *venia legendi* was taken from him and he could no longer talk to his students.

Beneath these bludgeonings of fate his head was "bloody but unbowed," and he came to London, 57 years old, with his wife and three young children. The one-

time professor of the leading hospital in Germany then had to go back to a course of study and sit his Finals in Scotland and qualify for the second time in 1937. Then, when he was approaching the age of 60, his second career had to commence. He practised in London, starting from a small nucleus of the English visitors who had consulted him in Berlin, and very soon his obvious sincerity and kindliness secured him an ever-widening circle of devoted patients. His face was a familiar one at scientific meetings, and he was always abreast of the times. There was none of the ruthlessness that is associated with the Teutonic system about him, but there was always the thoroughness which would often lead him to diagnose a case where others had failed.

He weathered many serious operations and illnesses, yet right up till his last seizure retained his freshness and youthful appearance, and his passing came as a great shock to all who knew him. At his funeral a beautiful farewell was pronounced by Professor Andrade, who turned again to Henley with lines that described him so well:

> "His face at once benignant, proud and shy
> His faultless patience, his unyielding will,
> Beautiful gentleness and splendid skill
> Innumerable gratitudes reply.
> His wise rare smile is sweet with certainties
> And seems in all patients to compel
> Such love and faith as failure cannot quell."

He had the joy of seeing his three children successful and happy in the land of their adoption. His widow stood by him in success and adversity, and helped him at every turn in his two careers, and to her and her children goes heartfelt sympathy in the loss of one to whom they always looked with admiration and affection.—A. D. W.

L. DEJARDIN, M.D.

We record with regret the death on January 14 of Dr. L. Dejardin, the distinguished Belgian surgeon.

Sir GORDON GORDON-TAYLOR writes: Few names can have been better known in the international domain of surgery during the past 20 years than that of Léo Dejardin, whose death took place in Brussels on January 14. He had been Sécretaire-Général of the International Society of Surgery since 1938, and his commanding presence at the meetings of the society was familiar to surgeons from all over the world. Dejardin has told us himself how Leriche had impressed upon him the weighty responsibility of the secretary-generalship of the society, and from filial piety towards the great French surgeon and a profound sense of duty towards the surgical organization to which he gave "le meilleur de lui-même" he imposed on himself the task of attending the many meetings of the various other surgical groups which to-day provide a forum for the digestion of new surgical pabulum, perhaps strengthen the ties between surgeons of various nations, even those from behind the Iron Curtain, and at any rate constitute a refresher course in the geography of Europe and elsewhere. There was always Dejardin: he carried by his very presence the oriflamme of the International Society of Surgery, whose prestige he had wholly dedicated himself to affirm.

Léonce Dejardin was born at Verviers on August 5, 1893, and had his schooling in that town. The outbreak of the 1914–18 war interrupted his medical studies, which he had commenced at Liège; he resumed them in Brussels at the close of hostilities. During his surgical lifetime he was first attached to the Ixelles Hospital, and later, from 1938 to 1954, he was chief of the surgical service of the Etterbeek Hospital in the Belgian capital. His relationship to the University of Brussels comprised a prosector's appointment in anatomy to Professor A. Dalcq, and from 1935 to 1949 he assisted Professor Danis in the teaching of surgical anatomy and operative surgery in the surgical department of the university. Dejardin was the author of some forty papers chiefly dealing with orthopaedic and vascular surgery; he was one of the *rapporteurs* on the subject of nerve injuries along with Wertheimer, of Lyons, and Merle d'Aubigné, of Paris, at the 49th Congrès de l'Association Française de Chirurgie (1946). As a surgeon he owed most to his old chief, Robert Danis, and to René Leriche, and he was one of the distinguished names, including Georges Duhamel, Evarts Graham, and Sir James Learmonth, who paid tribute in the recent volume (1956) *Hommage à René Leriche, par ses Élèves.*

No one could look on Léo Dejardin without sensing the soldier in him; he gained the Belgian Croix de Guerre in the 1914–18 war and the French Croix de Guerre for his activities in the "underground" movement in the 1939–45 Armageddon. He was a Commandeur de la Couronne and also an Officier de la Légion d'Honneur, and the entrance to the cemetery on the outskirts of Brussels was lined by a platoon of soldiers presenting arms to the cortège of a soldier making his last journey.

Great Britain did not forget Dejardin's services to surgery, for he was a Corresponding Fellow of the Association of Surgeons, and he became an Honorary Fellow of the Royal Society of Medicine on the same occasion as Lord Webb-Johnson. He was ardently Anglophile, and it was perhaps not unfitting that he should have drawn his last breath in a clinic that commemorates the life of service and the patriot's death of Edith Cavell.

Dejardin will be best remembered as the secretary-general of "The International." Surgeons will long recall this great-hearted giant, radiating happiness around him, the deep attractive voice, the expressive gestures of the restless hands. The man who ventures to assume a post, unpaid though it be, in an international organization must be under the special protection of Heaven if he escape the slings and arrows of hostile criticism, but who shall say that unworthy murmurings may not have diminished the powers of resistance of this noble frame, when illness descended upon him? For almost twenty years he had sacrificed private interests for the society round which his whole life was centred, and the French Legion of Honour, whose ribbon he proudly wore at all times, bespoke the honour of its wearer, for honour was the natural apanage of Léo Dejardin.

KIYOSHI SHIGA

Dr. K. Shiga, the distinguished Japanese bacteriologist, died at Sendai on January 25 at the age of 86.

Kiyoshi Shiga was born at Sendai on December 18, 1870, and graduated from Tokyo University in 1896. Two years earlier he had already begun to specialize in bacteriology, working as an assistant to S. Kitasato at the Institute for Infectious Diseases, Tokyo. In 1899, when this institute was taken over by the State and amalgamated with the university, Shiga was appointed director of the laboratory there, but not long afterwards he came to Europe and worked with Ehrlich at Frankfurt on the chemotherapy of trypanosomiasis. On his return to Tokyo in 1903 he joined Kitasato again in the latter's own institute. In 1919 he was appointed to the chair of infectious diseases at the University of Keio, in Tokyo, but later he moved to the Imperial University at Keijo-Seoul, Korea. After working for some years as professor of bacteriology there, he became dean of the faculty of medicine in 1929, and, later, chancellor of the university.

Shiga is best remembered for his discovery of the causal organism of bacillary dysentery, which he called *Bacillus dysenteriae* (*Zbl. Bakt.*, 1898, 1 Abt., **24**, 817 and 870). The genus was later named *Shigella* after him. He introduced a dysentery antiserum in 1900. Among his later work were studies of *Mycobacterium*

leprae. Shiga wrote several textbooks in Japanese on bacteriology, serology, and infectious diseases, contributed the section on bacillary dysentery in Osler's *Modern Medicine* (vol. 2, 1907), and wrote a short monograph in German on beriberi in 1911.

LEWIS M. TERMAN, Ph.D.

Dr. N. B. EASTWOOD writes: I have never seen in the medical press any article devoted to the problem of the education of the exceptionally gifted child; the education of the exceptionally unintelligent is a subject which is nearer to our hearts. It is one of the late Professor Terman's best achievements to have recorded in elaborate detail the fate of 1,500 highly gifted schoolchildren followed up for 25 years (*The Gifted Child Grows Up*, 1947, Stanford University Press. Volume 4 in the series "Genetic Studies of Genius"). This work is an obvious basis for thought concerning the education of the Newtons and Einsteins of the next generation. Your obituary conclusion (*Journal*, January 19, p. 170) that "he found that success in life depended more on emotional balance than on intellectual brilliance" introduces a false antithesis to which I believe Terman would not have subscribed. He found that his highly intelligent children were, on the whole, taller, heavier, more athletically successful, and above the general child population in character and personality. Far from making any contrast between emotional stability and intellectual brilliance, he found that the intellectually brilliant were, in fact, the emotionally stable and were also highly successful in their later careers. Your obituary notice may have intended to say that persons possessing an I.Q. of 135 and upwards possess sufficient intellectual endowment for most purposes, and that in this selected group of the population achievement may be considerably influenced by factors other than intelligence.

Dr. J. G. BIRD, physician to the Royal Berkshire Hospital, Reading, died on January 13 after a short illness, at the age of 63. Jason Grant Bird was born on November 4, 1893, at Bandon, Co. Cork, one of a family of nine. From Middleton College, Co. Cork, he went on to Trinity College, Dublin, where he took an arts degree in 1916 before graduating M.B., B.Ch. in 1918. He proceeded to the M.D. in 1920. After graduation he held house appointments at the Rotunda and Sir Patrick Dun's Hospital, Dublin, then becoming resident medical officer at Queen Mary's Hospital, Stratford, and the Dreadnought Seamen's Hospital, Greenwich. Later he saw service in Egypt for eighteen months in the R.A.F. Medical Service. In 1923 he settled in Reading, succeeding the late Dr. G. F. Murrell in general practice. Only three years after settling in Reading he became honorary secretary of the Oxford and Reading Branch of the B.M.A., a post he held for eight years. For many years he was physician in charge of the physiotherapeutic departments of the Royal Berkshire Hospital and of the Battle Hospital, Reading. In 1942 he was appointed assistant physician to the Royal Berkshire Hospital, and in 1948 he became consulting physician to the Reading hospitals and to the Oxford Regional Hospital Board. At the same time he retired from general practice. For many years he was county surgeon to the St. John Ambulance Brigade, and he was also associated with the work of the Medical Society for the Care of the Elderly, for geriatrics was a subject in which he developed a special interest. For 12 years he was a justice of the peace and served on the Reading bench of magistrates.

A colleague writes: By the death of Dr. J. G. Bird Reading has lost a highly skilled and experienced physician and an honoured citizen. After setting up in practice he became very well known as a genial and friendly doctor, and as a wise and kindly adviser with a very wide professional experience. A general physician of the old school, he was interested in medicine in its widest aspects, and many of his patients and colleagues will feel a unique sense of personal loss from his death. Dr. Bird's multifarious activities included fields other than medicine. He gave a great deal of time to committee and church work, and was an ardent supporter of Greyfriars Church, Reading, where he was a churchwarden for 24 years. Forthright and strict in his views and steadfast in purpose, he gave unstintingly of his time and energy in the cause of humanity, and he will long be remembered with warm affection by those who knew him. He took an interest in missionary work and was recently appointed chairman of the London City Mission. Among his other interests were the Reading Y.M.C.A. and the Reading Temperance Society, and he was a Friend of the University of Reading. In 1940 he married Miss Caryl Cobb and added family interests to his already full life. After moving two years ago to Gallows Tree Common, Oxfordshire, his health began to fail, but he continued to work until shortly before he died. He is survived by his wife and four children, to whom we extend our sincere sympathy in their loss.

Dr. W. A. M. SWAN, who practised for many years in north-west London, died on January 15 in Dublin, where he had been living in retirement since 1947. He was 76 years of age. William Aloysius Martin Swan was born on June 11, 1880. As a medical student in Dublin he had a brilliant career, being awarded the Carmichael medal for anatomy in 1906 and 1907. He qualified by taking the Irish Conjoint diploma in 1911. During the first world war he moved to London and was in partnership with Dr. A. T. Swan at South Hackney until 1921, and from then until 1947 on his own account in St. Pancras. He showed a great interest in local matters, especially medico-political affairs, and he served on the executive committee of the St. Pancras Division of the British Medical Association for some years, being chairman of the Division in 1930–1 and again in 1934–5. He also represented the Division at a number of Annual Representative Meetings. He leaves a married daughter and three sons, two of whom are doctors.

S. Y. writes: Dr. W. A. M. Swan was a conscientious and painstaking practitioner, and commanded great respect from his patients and colleagues. Although ten years have elapsed since he retired to live in Eire his contemporaries will remember him with affection, and with appreciation of his work. Many meetings of the St. Pancras Division's executive committee took place at his home, where both he and the late Mrs. Swan received us with charming hospitality.

Dr. KATHLEEN HANBY died suddenly and quietly on January 19 in a nursing-home, where she had been a patient for many weeks. She was 68 years of age. Kathleen Hanby was born on February 8, 1888, and came to England during the first world war from India, where she had had her medical training, graduating M.B. at the University of Calcutta in 1915. Her background was that of a cultured and intelligent family with distinguished connexions, keenly alive to the problems and movements of the day and with a strain of Irish fighter spirit on her mother's side.

G. J. writes: Kathleen Hanby became house-physician in the Hospital for Sick Children in Edinburgh in 1916, where I first met her as a fellow resident. The friendship then established was renewed when, in 1930, Dr. Hanby came to Manchester to prepare herself for general practice. She had spent the immediate post-war years as a school and tuberculosis officer in the midlands. For many years after taking up general practice Dr. Hanby had to contend against much illness, especially asthma, to which she became increasingly a victim. During the 1940–1 bombing period she lost her home and was herself injured, but went out into the street to help others. In spite of everything she

never lost heart for long, and her natural zest for living, her kindliness and quick brain, made her a delightful friend and interesting companion. She had outbursts of indignation over various subjects, to which her friends would listen amazed at the wide range of knowledge of history and facts she displayed, though usually unable to accept the sweeping condemnations made. She had great clinical acumen and skill, and deservedly won the love and confidence of many patients. The constant inflow of lovely flowers during months of illness gave ample testimony of this love. Dr. Hanby was retiring and shy of meeting strangers, and was little known outside the small circle of her local practice near Bolton. Hers was a quiet, unobtrusive, and courageous life, like that of many who give themselves devotedly to the service of their patients and have themselves to struggle against great odds. She made no contributions to medical literature and did nothing spectacular, but will long live in the memory and affection of those who, by intimate contact with her, could recognize the flashes of that fine and undefeated spirit that was herself.

Medical Notes in Parliament

Treatment of the Elderly Sick

When Parliament reassembled on January 22 after the Christmas recess Lord AMULREE, with the support of Lord COTTESLOE and Lord HADEN-GUEST, called attention in the House of Lords to the case of old people and administrative difficulties arising between the working of the National Health Service Act and the National Assistance Act.

He was concerned with the substantial minority of old people, mostly pensioners—and particularly those living alone—who were on the border between health and sickness, neither fit enough to look after themselves nor yet sick enough to need hospital treatment. The B.M.A. in 1947 set up a committee (of which he was a member) whose report advocated that old people who were not really ill, but frail and infirm, should come under the umbrella of the Health Service rather than being separated under the Assistance Act. Unfortunately that was not done, and the difficulties still remained. The Guillebaud Committee in 1956 reported that they were very worried about it. One suggestion, that there should be amending legislation to put the matter back under one authority, he dismissed as impracticable. Another that might be encouraged was that regional boards and local authorities should make a joint appointment when they appointed doctors to take care of the old people in their hospitals, so that they would have charge of the people under Part III of the Assistance Act. That had been done in one or two cases, and was working well. A third suggestion, which was included in the Guillebaud report, was that the welfare services might be transferred to the health committee of the local authority, which would mean that the medical officer of health would be in the chair and they would have a medical side to them. It was a medical matter, and the more that kind of balance could be kept the better.

Lord COTTESLOE, who is chairman of the North-west Metropolitan Regional Hospital Board, said that administrative difficulties arose mainly from the dichotomy under the two Acts, by which regional hospital boards were responsible for the aged sick and the county councils for the welfare of the senile and infirm. It was not a practical possibility to make a single authority, either local or hospital, responsible for the care of all the old people in an area. What was needed was not such a tidy, theoretical solution but a real understanding and knowledge of the problems and needs of the individual old people on the part of hospital officers on the one hand and the welfare officers and wardens of old people's homes on the other, and the closest co-operation between them locally. That was the course that should be pursued in the search for a solution.

Lord HADEN-GUEST advocated a national survey by a committee and the formulation of a plan for the country as a whole.

The EARL OF HOME, speaking for the Government, said that progress must rest on greater efficiency in organization, greater co-ordination of the efforts of hospitals, doctors, and welfare authorities, and greater appreciation by local authorities of the needs of the old. In spite of all that had been done, there was room for much better co-ordination between hospital and welfare authorities. He was inclined to think that the root of the trouble was the lack of accommodation for those who need no longer be kept in hospital, and that part of the trouble was lack of personnel to look after those old people in their homes. But some things could be done with advantage. One of them was Lord Amulree's suggestion about the joint appointment of geriatric physicians. Further attention ought to be given to the powers of local authorities to a direct meals service, in addition to assisting voluntary associations. There had been a survey between 1954 and 1956 by Ministry of Health officers and the services affecting the elderly sick. The results had been assessed on a national basis, and the Minister proposed to issue memoranda, with suggestions arising from the survey, to all hospitals and local authorities. No Government or Act of Parliament could compel co-operation, but if common sense was applied great improvements could be made.

Mental Hospital Patients

Mr. NORMAN DODDS (Erith and Crayford, Lab.) asked the Minister of Health on January 23 if he was aware of the concern that had arisen from the knowledge that a person could be certified as insane under the Lunacy Act, 1890, by one doctor at one interview lasting no more than five minutes, with the reasons for certification denied to the person concerned or to relatives: and what action was proposed to minimize the risk of mistakes, which could have a grave effect on the liberty of the individual, and to bring this aspect of national life more into keeping with modern practice. Mr. DENNIS VOSPER stated that he did not accept the implication. A summary reception order might be made by a justice of the peace on a certificate by one medical practitioner. It was for the justice himself to examine the person, to make inquiries, and to satisfy himself that the person was of unsound mind and a proper person to be detained. The law on this subject was being reviewed by a royal commission at the present time.

He informed Mr. Dodds that the numbers of persons detained under the Lunacy Acts were, in 1945, 130,462; in 1950, 120,698; in 1952, 117,948; and in 1955, 110,788. The numbers detained under the Mental Deficiency Acts were, in 1945, 55,336; in 1950, 59,417; in 1952, 61,211; and in 1955, 63,255.

Mr. DODDS asked how many persons in mental institutions, up to the latest convenient date, were detained under the Mental Deficiency Acts for other reasons than being mentally defective. Mr. VOSPER: I am not aware of any such persons. Mr. DODDS asked the Minister, in view of the large number of young people who had in the past been certified under the Mental Deficiency Acts because of being in need of care and attention rather than being mentally defective, and because of the difficulties that such patients had in invoking the law to have the certification set aside, what action he was taking to have a thorough investigation made of each case with a view to enabling as many as possible to lead normal and useful lives. Mr. VOSPER: I am not aware of any such persons.

Immigrants' Health Certificates

Captain H. KERBY (Arundel and Shoreham, Con.) asked the Minister of Health on January 25 if he was aware that Great Britain was the only Commonwealth country that any immigrant could enter without producing a certificate of good health; and what steps he proposed to safeguard

Great Britain from imported communicable diseases. Mr. VOSPER informed him that the existing Public Health (Ships) and (Aircraft) Regulations, 1952, gave wide powers to port medical officers to deal with any case or suspected case of communicable disease arriving in this country. In addition, alien immigrants might be medically examined under the Aliens Order, 1953.

February Meeting with Minister

The new Minister of Health, with the Secretary of State for Scotland, has agreed to meet representatives of the medical profession towards the middle of February. Mr. DENNIS VOSPER stated this in answer to three questions on January 28 asking for a statement on the salary negotiations. He added, "For the present, I have no statement to make."

Mr. ARTHUR LEWIS (West Ham, North, Lab.) asked for an assurance that the Minister would deal with the matter on its merits, and not treat the doctors in the same shabby and dirty way that the Government had treated M.P.s' salaries. Mr. M. LIPTON (Brixton, Lab.) suggested that, as the Government's honour was at stake, they should agree to arbitration to settle a firm basis for any future adjustment of doctors' salaries. Viscount HINCHINGBROOKE (South Dorset, Con.) spoke about the enormous importance of the State honouring its obligations to important sections of the community, and of seeing that justice, as pledged in the past, was fully discharged. He suggested that the Minister could argue with the Chancellor of the Exchequer that the possible inflationary consequences in the present instance could be taken care of by other means.

Mr. J. RANKIN (Glasgow, Govan, Lab.) asked the Minister if he was prepared to accept the contractual obligation implied in the Spens report on the basis of all future salary negotiations with the medical profession. Mr. VOSPER: I am advised that no legal contractual obligation exists. Mr. RANKIN said this was one of the points that had caused every scalpel in Scotland to be drawn over the week-end. There would be no satisfactory issue unless this matter was dealt with. Doctors did not accept the explanation which had been given. Mr. VOSPER: I am going to meet the doctors, and I shall be looking forward to that meeting. But I shall not meet them on the basis that a legal contractual basis exists.

Cigarette Smoking

Mr. LIPTON asked the Minister of Health whether he would move to appoint a select committee to consider what immediate and practical steps could be taken to reduce cigarette smoking. Mr. VOSPER replied "No." He did not consider that a select committee would be an appropriate body for this purpose. Mr. LIPTON questioned whether, as a definite connexion had been established between cigarette smoking and lung cancer, the hundreds of millions of pounds made by the Government out of cigarette smoking could be regarded as moral earnings. Were not the Government under a solemn obligation to warn the public of the risks? Should they not take more positive action, even if it meant upsetting the Chancellor and the tobacco magnates? Mr. VOSPER retorted that if Mr. Lipton had raised the matter in an adjournment debate, as he had said he would do, it would have been possible to deal with some of the rather unfair allegations he had made. Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked whether the evidence was not sufficiently strong for something definite to be done by the Ministry. Ought not young people and children in schools to be warned of the dangers of cigarette smoking? Mr. VOSPER said that he intended to look further into this, and take the advice of those concerned.

Pharmaceutical Products.—Discussions with the pharmaceutical industry on prices of proprietary preparations have recently been concluded, and in the light of these the industry has revised its proposals, which the Minister of Health is considering.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 12** (No. 2) and corresponding week 1956.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1957					1956				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	9	2	6	0	2	4	1	1	0	9
Dysentery ..	530	49	183	2		687	59	116	3	5
Encephalitis, acute	3	0		1		1	0		0	
Enteric fever:										
Typhoid ..	1	1	0	0	1	0	0	0	0	
Paratyphoid ..	4	1	1(B)	0		9	2	5(B)	0	
Food-poisoning ..	162	29	22	0		123	7		0	
Infective enteritis or diarrhoea under 2 years				12	13				12	6
Measles *	9,281	674	617	321	119	2,368	26	91	25	41
Meningococcal infection	35	3	7	0	3	33	3	17	1	1
Ophthalmia neonatorum	25	3	9	0		26	3	12	0	
Pneumonia † ..	648	39	417	11		897	83	387	12	1
Poliomyelitis, acute:										
Paralytic ..	47	7	2	0	17	35	4	6	2	4
Non-paralytic	25	3				24	3			
Puerperal fever § ..	224	32	5	1		208	33	13	1	2
Scarlet fever ..	528	33	84	13	19	714	31	93	38	13
Tuberculosis:										
Respiratory ..	543	57	124	16		574	61	91	13	
Non-respiratory	84	6	7	1		76	8	11	5	
Whooping-cough..	2 486	122	507	15	24	1,267	67	89	117	211

DEATHS in Great Towns	1957					1956				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	3	0	1	8	0	1	0	1
Influenza	21	0	0	0	0	48	6	5	2	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	1				0	1		
Pneumonia ..	348	39	28	17	12	488	96	30	10	12
Poliomyelitis, acute	5	1			0	3	0			0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	76	11	9	2	2	92	11	12	3	5
Non-respiratory		0	0	0	0		2	3	0	0
Whooping-cough..	1	0	1	0	0	2	0	0	0	1
Deaths 0–1 year ..	217	29	35	12	17	253	36	29	1	27
Deaths (excluding stillbirths) ..	6,023	831	617	142	177	7,383	1186	756	142	191
LIVE BIRTHS ..	8,525	1269	1118	252	410	7,903	1196	971	219	324
STILLBIRTHS..	205	31	18			226	33	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

London in 1955

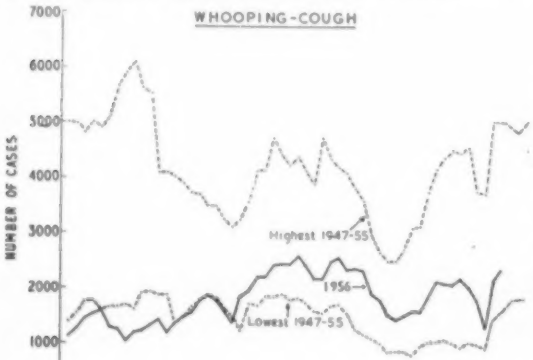
The population of the County of London in 1955[1] was 3,295,000, which was 27,000 fewer than in 1954. In comparison with England and Wales as a whole, there were relatively fewer people aged under 25 and over 44, with relatively more aged 25–44. Females exceed males by 6.5%, as compared with 3.7% in England and Wales. The live birth rate, at 15.1 per thousand population, was the lowest since the 1946 peak of nearly 21, but was well above the figures of the 1930's—about 13.5. It is much the same as the rate for England and Wales, though the proportion of women of child-bearing age is greater in London.

The general death rate was 11.5 per thousand population. It has not changed much since the end of the war, having fluctuated about one point above or below that figure. It is near the rate for England and Wales. The infant mortality rate, at 23.2 per thousand live births, showed a slight rise from the rate for 1954—namely, 20.6. The rate for London is normally lower than the rate for England and Wales, which in 1955 was 25.

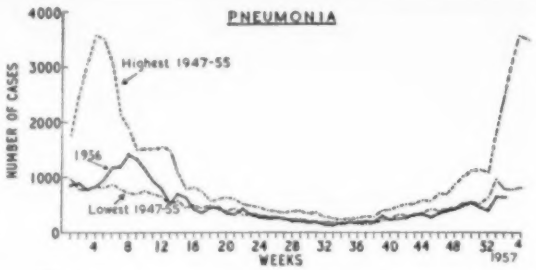
Cases of diphtheria were more numerous in 1955, being 16 as compared with 4 in 1954, and 2 deaths were reported. The County Medical Officer has recently started a campaign to increase the numbers of immunized children in London; only about 54% of children aged under 5 were immunized at the end of 1955. Other deaths caused by infectious diseases were 7 from whooping-cough, 15 from measles, 27 from diarrhoea in children aged under 2, 164 from influenza, 22 from meningococcal infections, 1 from erysipelas, 26 from acute poliomyelitis, and 561 from tuberculosis (517 respiratory). The commonest source of tuberculous infection nowadays is a human case; such was the source even in a recent outbreak among monkeys at the Zoo. B.C.G. vaccination is offered to all tuberculin-negative 13-year-old children attending London schools whose parents give written consent. By the autumn of 1955, 19,301 children had been vaccinated.

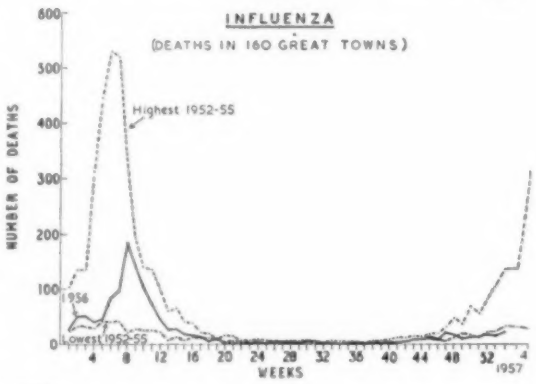
Graphs of Infectious Diseases

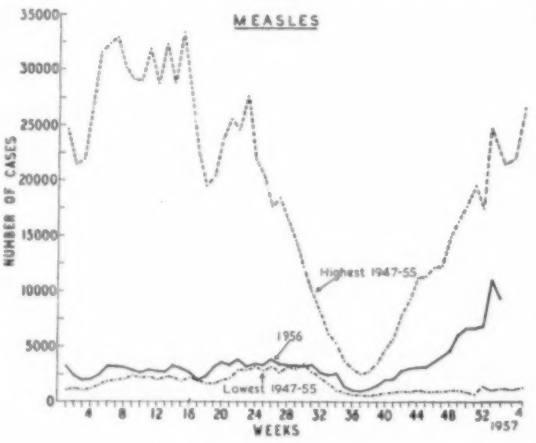
The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the years 1947–55 (influenza, 1952–5) are shown thus ------, the figures for 1956–7 thus ———. Except for the curves showing notifications in 1956–7, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



[1] *Report of the County Medical Officer of Health for the Year 1955* (L.C.C., 2s. 6d.).







Infectious Diseases

The only large variations in the returns of infectious diseases during the week ending January 12 in England and Wales were falls of 1,689 in the number of notifications of measles, from 10,970 to 9,281, and 44 for scarlet fever, from 572 to 528, and a rise of 377 for whooping-cough, from 2,109 to 2,486.

The largest falls in the incidence of measles were 453 in Lancashire, from 2,592 to 2,139, 346 in Yorkshire West Riding, from 919 to 573, and 324 in Essex, from 1,137 to 813; the only large rise was 151 in Northumberland, from 318 to 469. Only small fluctuations were reported in the trends of scarlet fever. The largest increases in the number of notifications of whooping-cough were 83 in Lancashire, from 215 to 298, 48 in Durham, from 109 to 157, 46 in Staffordshire, from 98 to 144, and 46 in Warwickshire, from 71 to 117. 9 cases of diphtheria were notified, being 7 more than in the preceding week.

72 cases of acute poliomyelitis were notified, and these were 3 more for paralytic and 6 more for non-paralytic cases than in the preceding week. The largest returns were London 10 (Battersea 2, Islington 2, Stepney 2), Surrey 10 (Reigate M.B.

7, Kingston-upon-Thames U.D. 2), Essex 7 (Dagenham M.B. 2), Kent 6 (Crayford U.D. 2), Sussex 6 (Hove M.B. 3), and Lancashire 5 (Bootle C.B. 2).

The notifications of dysentery numbered 530, being 5 fewer than in the preceding week. The largest centres of infection were Lancashire 110 (Accrington M.B. 27, Liverpool C.B. 14, Manchester C.B. 11, Bolton C.B. 10), Yorkshire West Riding 91 (Leeds C.B. 21, Sheffield C.B. 16, York C.B. 12), Warwickshire 74 (Coventry C.B. 66), London 49 (Woolwich 10), Staffordshire 22 (Kidsgrove U.D. 16), and Yorkshire East Riding 22 (Kingston-upon-Hull C.B. 20).

Channel Islands Census

At the 1951 census the population of the Channel Islands was 102,806 persons, an increase since 1931 of about 9,600. 2,066 visitors were enumerated in Jersey in 1951 and 1,131 in Guernsey and adjacent islands.

Householders were asked to state whether they had exclusive use of, or shared with another household, or were without a piped water supply within the house, a cooking stove or range, a kitchen sink, a water-closet, and a fixed bath. In Jersey 40% of all private households and in Guernsey and adjacent islands 36% had exclusive use of all five of these household arrangements. A further 8% in Jersey and 9% in Guernsey and adjacent islands had all except a fixed bath. These figures compare with 52% for England and 19% for Wales.

The populations of the islands were on the average slightly older than that of England and Wales. 12.6% of the population of Jersey were aged 65 and over, and 12% in Guernsey and the adjacent islands. The figure for England and Wales was 11.0%. Since 1931 the proportion of married people has increased particularly among young people. At age 20–24, in Jersey, there were 245 married males per thousand as compared with 168 in 1931, and 461 married females per thousand compared with 291. In Guernsey and the adjacent islands the changes were similar. Fertility in Guernsey was higher than in Jersey. In Guernsey and the adjacent islands there were 186 live-born children per 100 married women under age 50, while in Jersey the figure was 167. In England and Wales it was 169.

Week Ending January 19

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 693, whooping-cough 2,664, diphtheria 4, measles 8,175, acute pneumonia 516, acute poliomyelitis 41, dysentery 477, paratyphoid fever 2, and typhoid fever 5.

Medical News

Benefactions by the Wellcome Trust.—This week the Wellcome Trustees announce grants totalling £173,500 to scientific institutions in Britain. In addition, the Trustees have agreed in principle to present a motor cruiser to the Medical Research Council to assist communication between the Council's laboratories at Fajara on the Gambia River and the branch laboratory near the village of Keneba, some 70 miles further up the river. This vessel would be adaptable as a mobile research laboratory for use in field studies in the interior of the Gambia territory. Appropriately enough, as the Trustees point out, probably the first floating laboratory to be made was the one built in 1907 to the order of the late Sir Henry Wellcome. It was used on the Nile by members of the staff of the Gordon Memorial Hospital, Khartum. Details of the grants to scientific institutions are as follows:

Leeds University.—Up to £60,000, towards building research laboratories for medical physics and urology on the site of the General Infirmary.

Edinburgh University.—Up to £35,000, for rebuilding animal houses at the Institute of Animal Genetics.

Royal College of Surgeons of England.—Up to £35,000, for the completion of the Wellcome Museums at the College.

Manchester University.—Up to £13,000, for a mobile radiographic and laboratory unit for use primarily in field work on the rheumatic diseases.

St. Andrews University.—Up to £15,000, for adding Wellcome Laboratories of Pharmacology to the Gatty Marine Laboratory.

Rowett Research Institute, Aberdeen.—Up to £5,000, for a building to house special equipment for research in animal nutrition.

University College of South Wales and Monmouthshire, Cardiff.—Up to £3,000, for an ultracentrifuge for indefinite loan to the department of biochemistry.

Liverpool Medical Institution.—£5,000 spread over five years, for cataloguing the library and rebinding books published before 1850.

Royal Faculty of Physicians and Surgeons of Glasgow.—£2,500 spread over five years, for rebinding historical volumes in the library.

Caesium Unit at Royal Marsden Hospital.—The radiotherapy department of the Royal Marsden Hospital is carrying out a clinical trial of radioactive caesium as a source for beam therapy at its branch hospital, the Downs Hospital, Sutton. The unit, which was designed by Professor W. V. MAYNEORD, is the second of its kind in the world, the first being at Oak Ridge, Tennessee; another unit, at Southampton, with a rotating apparatus containing two caesium sources, is expected to start work in a few months' time. The caesium comes as a waste product from the Atomic Energy Authority's reactor at Windscale, where it is extracted by a complicated chemical process and sealed in platinum capsules. The active material is the 137-isotope which emits gamma rays. The caesium source has a number of advantages over the usual 250-kilovolt *x*-ray therapy machine: the quality of its beam, with the energy concentrated over a very narrow waveband of short wavelength, is about equivalent to that produced by the much more costly 660-kilovolt machine; as a consequence, absorption is much more even in the various tissues and there is little trouble from differential absorption in bone; the risk of damage to the skin is also less. On the other hand, the amount of protection needed is far less than with a cobalt-60 source, a factor of importance in the design of both the treatment room and the container for the caesium; the apparatus is thus more manœuvrable and better adapted for treatment at short distances, such as for tumours in the head and neck. In spite of these advantages, the caesium unit is also attractive economically. Its capital cost is about the same as for a conventional *x*-ray therapy plant—there is even a considerably cheaper "utility" model available—and, apart from the hire of the caesium, running costs are negligible. The trial is under the direction of Professor D. W. SMITHERS.

Teaching Hospital in the West Indies.—In September, 1952, the Teaching Hospital of the University College of the West Indies was opened with 240 beds. The hospital is in Jamaica. The intention of the Jamaican Government, as stated in a law establishing it in 1948, was a 500-bed teaching hospital for the instruction each year "of not less than thirty medical students in such subjects as are usually provided in medical schools forming part of the University of London." January, 1955, was given as the deadline. Since the hospital was opened a further 81 beds have been added, "provisional recognition" has been accorded by London University, and plans have been prepared for further expansion. A report has been published (Colonial No. 327, H.M.S.O., price 2s. net) giving the views of a four-man committee, appointed by the Colonial Secretary, on the hospital's future development. The committee consisted of Dr. R. S. AITKEN, vice-chancellor of Birmingham University (chairman); Dr. E. R. BOLAND, dean of Guy's Hospital Medical School; Dr. J. W. P. HARKNESS, medical adviser to the Comptroller for Development and Welfare in the British West Indies; and Mr. G. A. PHALP, secretary to the United Birmingham Hospitals. Their principal recommendations are that the teaching hospital should be enlarged to provide for fifty students in each of three clinical years, a recommendation which would involve bringing the number of beds up to 454 at a capital cost of £1m.; and that the hospital's board of management should be increased so as to include members

from British Caribbean territories other than Jamaica and one member of the hospital medical staff besides the dean. Recommendations are also made about recurrent costs.

Report of an Accident.—The United States Atomic Energy Commission has published a report on the medical findings among the Marshall Islanders and members of the American task force who were accidentally contaminated by the hydrogen bomb exploded at Eniwetok in March, 1954. The report, edited by Dr. E. P. CRONKITE, Dr. V. P. BOND, and Dr. C. L. DUNHAM, is titled, *Some Effects of Ionizing Radiation on Human Beings*, and may be obtained from the U.S. Government Printing Office, Washington, 25, D.C., for $1.25. The report runs to 106 pages, and includes as its final chapter a general discussion on radiation injury from atomic weapons. The accident was due to an unexpected change in the wind.

Scholarships Abroad.—The British Council announces about a hundred scholarships for British students (mostly university graduates or undergraduates) for study abroad. They provide for free tuition and maintenance, usually for a full academic year. The British Council helps with the recruitment of candidates, and further details may be obtained from the controller of the council's education division, 65, Davies Street, London, W.1.

Active Membership of W.H.O.—The Government of Poland has now informed the World Health Organization of its desire to resume active membership. Similar requests by Albania and Bulgaria were noted in this column last week (p. 237). Poland's active participation lapsed in August, 1950.

W.H.O. Regional Director for Europe.—Dr. P. J. VAN DE CALSEYDE, director-general of public health at the Belgian Ministry of Health, has been appointed director of the World Health Organization's regional office for Europe from February 1. He succeeds the late Dr. NORMAN BEGG.

Osler Club.—At a meeting on January 24 at the Royal College of Physicians, Sir RUSSELL BRAIN, P.R.C.P., gave an address on Dr. Thomas Lawrence (1711–83), a former president of the College and a friend of Dr. Samuel Johnson. Dr. W. S. C. COPEMAN, the Club's president, was in the chair. An exhibition of historical books, papers, and portraits was held subsequently in the library.

North of England Obstetrical and Gynaecological Society.—At the annual meeting on January 18 the following were elected officers for 1957: president, Mr. F. STABLER; vice-presidents, Dr. E. A. GERRARD (Manchester), Mr. P. MALPAS (Liverpool), Mr. H. AGAR (Leeds), Mr. G. R. MACDONALD (Sheffield), and Dr. W. HUNTER (Newcastle); hon treasurer, Mr. C. H. WALSH; hon. general secretary, Mr. F. J. BURKE; and hon. reporting secretary, Miss U. M. LISTER.

Postgraduate Medical Studies at Oxford.—Surgeon Rear-Admiral J. HAMILTON is the director of Postgraduate Medical Studies at Oxford, not Dr. JANET VAUGHAN and Dr. G. E. F. CHILVER as we stated on January 19 (p. 179). They have been appointed to the board of electors for the directorship.

Professor W. C. W. Nixon, professor of obstetrics and gynaecology at University College Hospital, London, has been appointed to the World Health Organization's expert advisory panel on maternal and child health.

COMING EVENTS

Lecture in Belfast.—Sir CECIL WAKELEY will deliver the Sir Thomas and Lady Edith Dixon Lecture at the Royal Victoria Hospital, Belfast, on Friday, February 8, at 4.30 p.m. His subject will be "External Herniae."

Corneo-plastic Unit, East Grinstead.—Lecture-demonstrations to illustrate the relationship of ophthalmic and plastic surgery will be held on February 2, March 2, March 9, and April 6 at 2 p.m. Details from the secretary, Corneo-plastic Unit, Queen Victoria Hospital, East Grinstead.

Tenth International Hospital Congress.—Lisbon, June 3–7. Registration before March 15. Details from Captain J. E. STONE, 10, Old Jewry, London, E.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 4

MARLBOROUGH DAY HOSPITAL.—8.15 p.m., Dr. T. F. Main: The Past and the Present in Neurosis.

●UNITED HOSPITALS CATHOLIC SOCIETY.—At 13, Devonshire Place, W., 6.15 p.m., Mr. A. J. King: Marriage—Moral and Medical Concepts.

Tuesday, February 5

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. N. B. Myant: Biliary Excretion of Thyroid Hormone.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. T. Brain: Electrotherapeutic Techniques.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Dr. J. T. Scales: Metals and Plastics in the Treatment of Disease.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Milroy Lecture by Dr. D. D. Reid: Environmental Factors in Respiratory Disease.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Erasmus Wilson Demonstration by Dr. G. T. Allen: Histological Variations in Basal Cell Tumours.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. D. W. S. Gordon: Some Unusual Lesions of the Vulva.

Wednesday, February 6

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Presidential Address by Dr. K. Shirley Smith: Revision of Underwriting Standards in Life Assurance.

EDINBURGH CLINICAL CLUB.—4 p.m., visit to Department of Cardiology, Edinburgh Royal Infirmary.

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—7.30 p.m., meeting with Queen Margaret Medical Society. Professor Ian Donald: The Dominant Sex.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Laboratory Procedures for Mycotic Infections.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. T. Holmes Sellors: Surgical Treatment of Pulmonary Stenosis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m. Mr. H. G. Hanley: Disorders of Micturition in Females.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Professor J. H. Dible: Pathology of Peripheral Ischaemia.

MIDLAND MEDICAL SOCIETY.—At 154, Great Charles Street, Birmingham, 8.15 p.m., Dr. H. W. Donovan, Dr. C. F. Hawkins, Professor E. Brodie Hughes, and Dr. L. Nagley: Symposium on the Relief of Pain.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. Alick Isaacs: Influenza and Adenoviruses.

ROYAL MEDICAL SOCIETY EDINBURGH.—8 p.m., clinical meeting.

Thursday, February 7

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. H. M. Sinclair: Vitamins in Nutrition.

FACULTY OF HOMOEOPATHY.—5 p.m., Dr. L. R. Twentyman: Approach to the Pre-cancerous State; Dr. A. E. Stringer: Review of Treatment of Pneumonia and Acute Bronchitis in Children Admitted to the Royal London Homoeopathic Hospital Since 1948.

NORTHAMPTON MEDICAL SOCIETY.—At Northampton General Hospital, 3 p.m., clinical meeting.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Milroy Lecture by Dr. D. D. Reid: Environmental Factors in Respiratory Disease.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. H. Paterson: neurology demonstration.

ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY.—4.30 p.m., demonstration and discussion of clinical cases.

UNIVERSITY COLLEGE LONDON.—At Eugenics Theatre, 5 p.m., Mr. D. J. Payne: Compensation for Industrial Injuries.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.15 p.m., Professor F. Bergel, D.Phil.Nat., Ph.D., D.Sc., F.R.I.C.: Chemical Aspects of Psychopharmacology.

Friday, February 8

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. D. I. Williams: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. K. Robson: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. C. Gill-Carey: Tinnitus.

MIDLAND CENTRE FOR NEUROSURGERY.—At Holly Lane, Smethwick, near Birmingham, 8 p.m., Sir Francis Walshe, F.R.S.: Aetiology and Nature of the So-called Traumatic Neuroses.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Professor F. R. Winton: Renal Circulation.

ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., talk by Dr. R. M. Marquis: Impact of Surgery on Cardiology.

●UNITED KINGDOM COMMITTEE FOR THE WORLD FEDERATION FOR MENTAL HEALTH.—At County Hall, S.E., 5.45 p.m., Dr. Margaret Mead: Mental Health in a Changing World.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Griffiths.—On January 14, 1957, at the Imperial Nursing Home, Cheltenham, Glos, to Elizabeth (formerly Poulton), wife of Dr. Eric Griffiths, a brother for Lynn—Anthony Eric.

Spalding.—On January 1, 1957, at Oxford, to Dr. Elizabeth (formerly Falle) and Dr. John Spalding, a daughter.

Way.—On January 19, 1957, at the C.S.I. Hospital, Karim-Nagar, India, to Dr. Hedi Way (formerly Papigay), wife of Dr. Gilbert Way, a sister for David—Erica Ruth.

DEATHS

Pittman.—On January 19, 1957, John Cecil Pittman, M.B., B.S.

Thomas.—On January 11, 1957, at 80, Chatsworth Road, Croydon, Surrey, Rufus Clifford Thomas, F.R.C.S.Ed., F.R.C.O.G.

Wilson.—On January 5, 1957, William Mitchell Turner Wilson, M.B., Ch.B., of 951, Harrow Road, Wembley, Middlesex, aged 73.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

"Spanish 'Flu"

Q.—*What is the "Spanish 'flu" mentioned recently in the newspapers, and why is it so named? Is it true that it carries a particularly high mortality, and, if so, what is the reason for this?*

A.—The term "Spanish 'flu" was at one time applied to the virulent form of influenza which afflicted the whole world in 1918–19. The term was a misnomer, as there is no reason to believe that the disease came from Spain. It did cause a high mortality, particularly in young adults. This was due to pneumonia in which various secondary infecting organisms were involved. There is no reason to believe that such a virulent strain of influenza has been current in recent years.

Cancer Hazard from Tar Lotions

Q.—*There is no doubt that coal tar contains carcinogens, yet why is it that many dermatologists still persist in using tar preparations for chronic dermatitis and eczemas? These conditions themselves predispose to carcinomatous changes.*

A.—Although it is true that coal tar contains carcinogens, in the concentrations usually used its carcinogenic effects are negligible. There are probably very few dermatologists who avoid the use of tar as an antipruritic because they fear the development of malignancy. We see very many patients who have used tar lotions and ointments over many years, yet the development of tar dermatoses and malignant changes is of the greatest rarity. A few cases have been recorded of carcinoma developing in the skin after long-continued application of tar, but this happens so seldom that one may indeed doubt whether the tar has had much to do with it.

Coal-tar applications are extremely valuable for the relief of irritation, and it seems entirely reasonable to suppose that their value more than offsets this very small risk. Incidentally, it is very doubtful whether chronic dermatitis or eczemas have the slightest tendency towards malignant change.

Two Attacks of Tetanus

Q.—*A boy of 10 with chronic otorrhoea, living in India, has had two very severe attacks of typical tetanus separated by a year's interval. Both attacks were treated by large doses of antitoxin. (1) How long is the usual immunity after an attack of tetanus, and are second attacks common? (2) Could the aural infection have had any bearing on the attacks, and, if so, what treatment is advised for it? (3) Should active immunization with tetanus toxoid be undertaken after an attack of tetanus; if so, how soon, and what dosage scheme is recommended? At what intervals should boosting doses of toxoid be given?*

A.—(1) The evidence suggests that the immunizing effect of a clinical attack of tetanus is very slight.[1 2] Repeated attacks have been known to occur in the same person, but they are very uncommon.

(2) An infection of the middle ear is a well-known source of tetanus infection. Basic treatment should consist in eradication or drainage of the infected focus after active or passive immunization, but the actual procedure should be varied to suit the individual patient. A chronic middle-ear infection, secondarily infected with tetanus bacilli, might well give rise to two attacks of tetanus separated by a long interval. Such a case was described in a letter by Dr. Trevor Phillips recently.[3] The mechanism is probably as follows: A large dose of antitoxin would neutralize circulating toxin and allow natural recovery from tetanus to take place and symptoms to subside. However, spores remaining in the wound might germinate later and produce a further clinical attack of tetanus which would again subside with antitoxin treatment.

(3) Although second attacks of tetanus are rare, active immunization is the only certain way of preventing them. Payling Wright and his colleagues[4] have pointed out that the previous injection of a soluble antigen leads to its much faster removal from the circulation on subsequent injection, an action that reduces the therapeutic effect of second doses of antitoxin. They therefore recommend that once a person has received an injection of a horse-serum antitoxin, irrespective of the disease for which it may have been given, that person should be promptly immunized against diphtheria and tetanus with the appropriate toxoid. However, it is wise to delay active immunization until after the injected antitoxin has had a chance to be eliminated—a process which should not take longer than six months. The method of initial active immunization recommended by the Army Pathology Advisory Committee[1] consists of two injections of tetanus toxoid, spaced by not less than 6 weeks but not more than 12 weeks, followed by a third injection 6 to 12 months later. A reinforcing dose is usually given every five years.

REFERENCES

1. Barr, M., and Sachs, A., *The Investigation into the Prevention of Tetanus in the British Army*. Army Pathology Advisory Committee. Report, 1956, War Office, London.
2. Parish, J. H., *Antisera, Toxoids, Vaccines, and Tuberculins*, 1954, 3rd ed. London.
3. *British Medical Journal*, 1956, **2**, 714.
4. Littlewood, A. H. M., Mant, A. K., and Wright, G. Payling, ibid., 1954, **2**, 444.

Granuloma Annulare

Q.—*What is known of the aetiology of granuloma annulare, and how should the condition be treated?*

A.—The cause of granuloma annulare is completely unknown, and recent views about its aetiology involve abandonment of former ideas rather than the acceptance of new ones. For example, the tuberculous aetiology has been entirely given up, and although the histopathology shows some resemblances to that of the rheumatic diseases there is no clear relationship between the two conditions.

For most dermatologists views on treatment have tended to undergo a somewhat similar change. The tendency now is to leave the lesions untreated; it is known that they clear up eventually without scarring and that there are no systemic complications of any sort. Most methods of treatment involve physical destruction, which leads to scarring and is hard to justify. Carbon dioxide snow is favoured by some.

Prognosis in Treated Pernicious Anaemia

Q.—*What is the prognosis for patients with pernicious anaemia treated with adequate amounts of vitamin B_{12}? Are they ever cured in the sense that treatment is no longer necessary?*

A.—The introduction of vitamin B_{12} (cyanocobalamin) is too recent for there to be reliable statistics on survival and morbidity among patients with pernicious anaemia treated with the pure vitamin. Clinical observation, however, suggests that such patients have an expectation of life and a morbidity no worse than that of the general population: in fact, it has been suggested that they may be better off, because they come under review every month or two when they receive their injections.

In his presidential address to the Manchester Medical Society last October Dr. J. F. Wilkinson reviewed a personal series of 2,211 cases of pernicious anaemia seen over the past 28 years. Of course, only in the last few years would pure vitamin B_{12} have been available for the treatment of these patients, but the mortality in this series was only 0.83% per year. Almost all died from conditions other than pernicious anaemia; but, of those who died of cancer, in about half the primary was in the stomach. In Dr.

Wilkinson's experience the expectation of life for the patients in this regularly supervised group of patients was rather better than for people without pernicious anaemia. Of the 1,550 patients still attending his clinic, no fewer than 758 were over 70 years of age, 283 over 80 years, 39 over 90, and one over 100.

Patients with pernicious anaemia are never cured in the strict sense of the word, though if adequately treated their lives are in every respect as if they had been. The chief pathological change is the atrophy of the gastro-intestinal mucosa, which so far has proved irreversible. Very occasionally a patient who discontinues treatment remains well for months or even years before relapsing, but these are exceptional cases and afford no general grounds for the discontinuance of treatment. Treatment must be for life.

Nasal Sprays for the Common Cold

Q.—*Manufacturers continue to advertise nasal sprays of one sort or another, some of them containing sulphonamides, antibiotics, hydrocortisone, or vasoconstrictors, for the treatment of the common cold. Is it advisable to use any or all of these medicaments in this way?*

A.—The use of nasal sprays containing sulphonamides or antibiotics is to be deplored, on account of the grave danger of sensitization which it incurs. A patient who has used a nasal spray of this sort for a relatively trivial condition may find that subsequent use of the antibiotic or sulphonamide for the treatment of a serious disease is made difficult or impossible by a sensitivity reaction. With regard to hydrocortisone, there may be a place for the use of this in the management of severe vasomotor rhinitis, seasonal or otherwise, but its use in infections of the common-cold type may, in theory, increase the risk of secondary bacterial infection. Vasoconstrictors may give temporary relief to nasal congestion and obstruction, but in the early acute stage of a cold this relief is transient and may be followed by aggravation of the symptoms. Later, when secondary bacterial infection has given rise to a purulent phase with involvement of the nasal sinuses, vasoconstrictors may be useful in permitting intermittent drainage of secretions from the affected sinuses.

Injury and Central Retinal Vein Thrombosis

Q.—*Can an injury produce thrombosis of the central retinal vein or one of its branches?*

A.—Central retinal vein thrombosis has been reported after a contusion as a rarity (von Wiser, 1901; Hillemans and Pfalz, 1905; Pincus, 1907; Cozzoli, 1916).[1]

REFERENCE

[1] Quoted by Duke-Elder, S., *Textbook of Ophthalmology*, vol. 6, p. 5854, 1954. London.

Sensitivity to Arsenic and Penicillin in Tertiary Syphilitic

Q.—*A patient with tertiary syphilis is sensitive to arsenic and penicillin. How should he now be treated?*

A.—Most of the antibiotics derived from lower-grade fungi are effective in the treatment of primary, secondary, and tertiary syphilis, and attempts to desensitize patients who have become intolerant of arsenic and penicillin, besides being often unsuccessful, are unnecessary.

A ten-day course of oxytetracycline or chlortetracycline (0.5 g. six-hourly) is recommended. The dosage suggested by some workers, including Taggart and his collaborators,[1] is 60 mg. per kg. of body weight daily for six to eight days. Antibiotic therapy should be followed by a ten-week course of intramuscular injections of bismuth (injectio bismuthi, *B.P.*, 1.5 ml. once weekly), and, as iodides assist materially in the resolution of tertiary lesions, a mixture containing potassium iodide, 15 gr. (1 g.), should be taken three times a day at the same time.

REFERENCE

[1] Taggart, S. R., Romansky, M. J., and Landman, G. C., *Amer. J. Syph.*, 1952, **36**, 174.

NOTES AND COMMENTS

Retraction of the Prepuce.—Dr. A. E. SELIGMANN (Barking) writes: I was glad to read your expert's opinion ("Any Questions?" December 8, 1956, p. 1382) that it was doubtful if the practice of gentle retraction of the prepuce from 6 months onwards would affect the incidence of necessary circumcisions. Even during the first six months it is unusual for the prepuce to be left alone, and among hundreds of male babies seen at infant welfare clinics I have not yet met one whose mother has been taught to respect the waiting period of six months. On the other hand I was surprised to learn that "most prepuces will retract spontaneously by the age of 2 or 3 years." As a school medical officer I have seen an appreciable number of school-entrants with fully or half-adherent prepuces. In some cases mothers have even told me that the boy "had been done" as a baby, that she had been unable to persevere with it, and that the foreskin had become "stuck again" (if it was ever mobilized in the first place). I suspect that these late adherent cases do right themselves spontaneously after a few more years. Or do medical officers in the Forces still see many adherent cases?

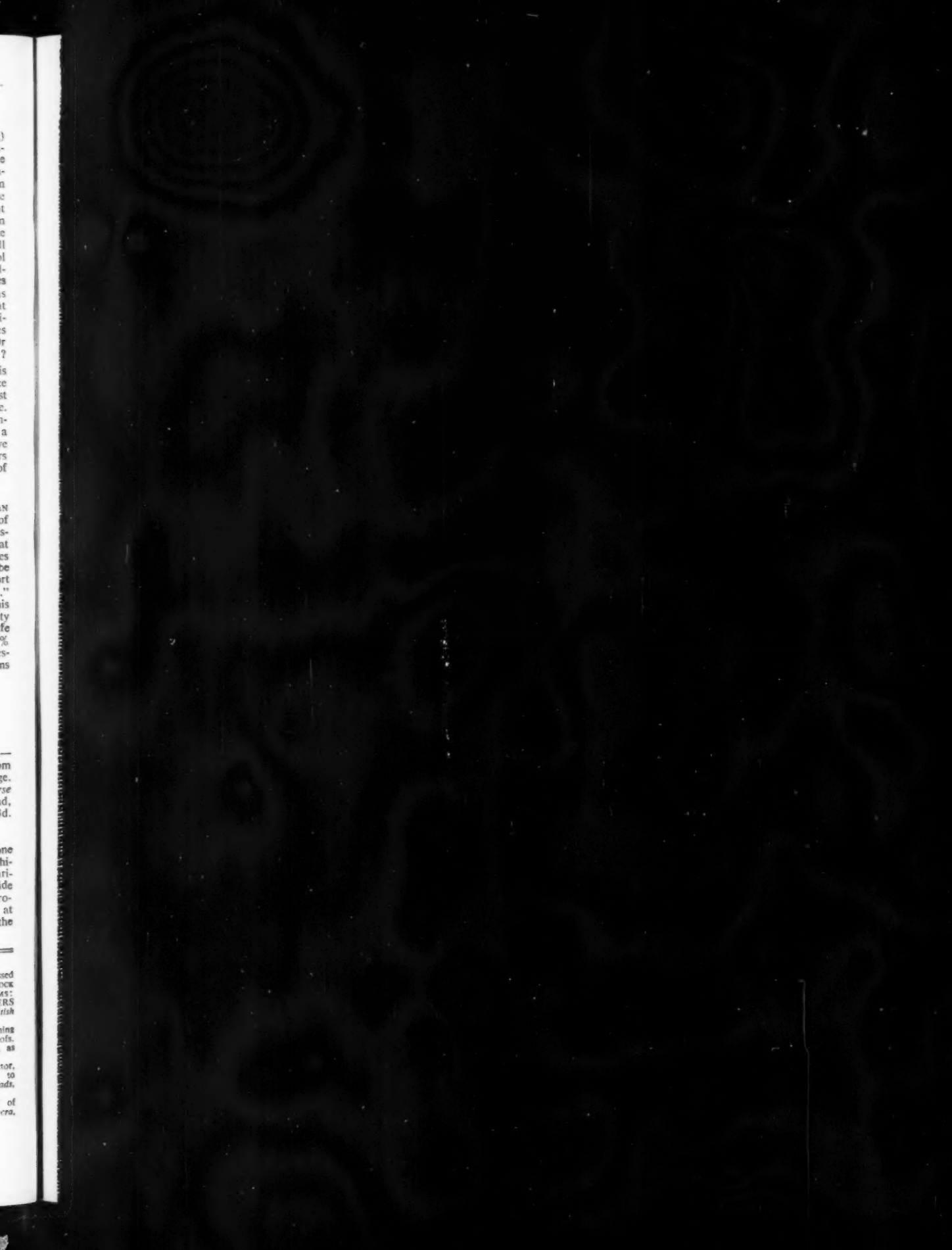
OUR EXPERT replies: Dr. Seligmann is clearly correct in his observations about adherent prepuces in boys at school-entrance age. In my answer to the original question I said "most prepuces" will retract spontaneously by 2 or 3 years of age. This was certainly not meant to exclude the "appreciable number" encountered by Dr. Seligmann. There are inevitably a number which take longer—and a few which will require active intervention. The answer to the question whether medical officers in the Forces will see many cases depends on the definition of "many." They certainly see "a few."

Lignocaine in Pudendal Block for Low Forceps.—Dr. NORMAN MORRIS (London, W.12) writes: An answer discusses the use of 0.5% lignocaine for pudendal block anaesthesia ("Any Questions?" December 29, 1956, p. 1559). Whilst advising that usually less than 80 ml. will prove adequate, nevertheless it states that "the maximum amount of this concentration that may be safely given is 200 ml." Dutton,[1] however, in another report recommends 50 ml. of 0.5% lignocaine as "effective and safe." The majority of obstetricians would, I think, agree with this statement. Hunter[2,3] has made a careful study of the toxicity of lignocaine, and he considers that 500 mg. is the maximum safe dose, even when adrenaline is added—that is, 100 ml. of an 0.5% solution. It would be a great pity if this extremely useful anaesthetic and method fell into disrepute because of complications resultant upon unnecessary overdosage.

REFERENCES

[1] Dutton, W. A. W., *Lancet*, 1955, **2**, 1368.
[2] Hunter, A. R., *Brit. J. Anaesth.*, 1951, **23**, 153.
[3] —— *Lancet*, 1956, **1**, 158.

Books of "Any Questions?" and Refresher Course Articles.—The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices include postage. *Any Questions?*, Volumes 2 and 3 (8s. each); *Refresher Course for General Practitioners*, Volumes 2 and 3 (26s. 6d. each inland, 26s. overseas); *Clinical Pathology in General Practice* (22s. 3d. inland, 21s. 9d. overseas).

Correction.—In Dr. M. M. Glatt's letter on methyprylone (*Journal*, January 19, p. 164) the sentence beginning "Glutethimide ('doriden,' methyprylone and α-phenyl-α-ethyl glutarimide) . . ." should read: "Methyprylone and glutethimide (α-phenyl-α-ethyl glutarimide, 'doriden'), another recently introduced non-barbiturate hypnotic, are both used in many wards at the Warlingham Park Hospital as satisfactory alternatives to the barbiturates."

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